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PERIVESICAL INSUFFLATION OF GAS FOR DETERMINATION OF BLADDER WALL THICKNESS IN TUMORS OF THE BLADDER

by

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The correct surgical approach to tumors of the urinary bladder is dependent to a great degree on the preoperative evaluation of their degree of malignancy. Biopsy often affords the correct diagnosis, but in some cases it may be misleading if the portion studied is not representative of the tumor as a whole.

The general appearances (shape, surface and borders) of a bladder tumor may, as FRANKSSON, LINDBLOM & WHITEHOUSE (1956) pointed out, provide some indication of its degree of malignancy. According to these authors, tumors with ill-defined contours are usually more malignant than those which are sharply delimited, and the same applies to solid and sessile tumors in comparison with papillomatous and pedunculated types. Thus, examination of the intravesical parts of a tumor by cystoscopy and cystography may give an early indication of the degree of malignancy.

The criterion of a malignant tumor is infiltrative growth. It may be possible to establish the presence or absence of deep infiltration by palpation under anesthesia and by a roentgenographic study of the bladder wall thickness at the site of tumor. The value of the former method has been analyzed by NILSSON

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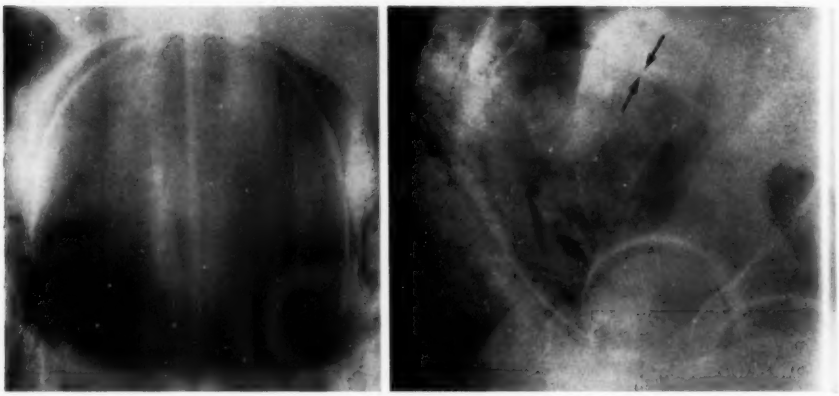

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Fig. 1. Case 1. Normal case. a) Tomogram a.p. b) Lateral. The thickness of the bladder wall (←) is defined by the intra- and perivesical gas.

(1958), who pointed out that with palpation under spinal anesthesia it is possible to evaluate the degree of malignancy only of tumors situated in the lateral wall of the bladder.

Roentgenologic determinations of the bladder wall thickness may be performed with or without perivesical injection of contrast medium. FRANKSSON & LINDBLOM (1952) in 55 of 117 cases of bladder tumors, were able to estimate the bladder wall thickness by means of the perivesical fat; in some cases they also injected Perabrodil into the prevesical space. With the latter method, however, it is possible to evaluate only the anterior basal portions of the bladder wall. TRUC et coll. (1951), CAMERINI et coll. (1953), LUZZATTI & GALDINI (1957), and others, studied the thickness of the bladder wall by injecting oxygen into the prevesical space and gas into the bladder. These methods may, of course, be implemented in suitable cases by examination of organs contiguous to the bladder, as for example the colon or loops of small intestine situated in the true pelvis. The part of the bladder which is invested by peritoneum can be examined following pneumoperitoneum.

In those cases of bladder tumor, in which a study of the perivesical fatty layer alone has not enabled us to evaluate the bladder wall thickness, we have for more than two years resorted to perivesical insufflation of gas following puncture of the prevesical space. Although our series is small, we are reporting the results, because so far as we are aware no systematic analysis, with correlation of bladder wall thickness as observed roentgenologically by this method and biopsy findings, has previously been reported.

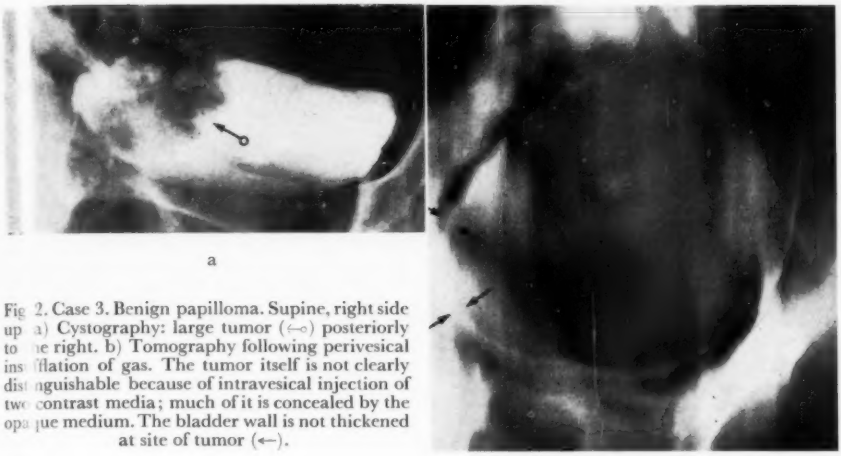

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Fig. 2. Case 3. Benign papilloma. Supine, right side up. a) Cystography: large tumor (←○) posteriorly to the right. b) Tomography following perivesical insufflation of gas. The tumor itself is not clearly distinguishable because of intravesical injection of two contrast media; much of it is concealed by the opaque medium. The bladder wall is not thickened at site of tumor (←).

Technique

A catheter is introduced into the bladder, which is emptied as completely as possible. The patient lies supine with the feet slightly raised. Following local anesthesia an injection needle is introduced immediately above the symphysis pubis and directed caudally and dorsally. Its tip should lie about one centimeter behind and below the upper border of the symphysis and its position checked roentgenographically or fluoroscopically. After great care has been taken to ensure that the needle tip has not entered a vessel, about 700 to 800 ml oxygen are injected. The patient is then placed in various positions so that the gas may diffuse round the bladder. When the examiner has satisfied himself on this point, and carbon dioxide has been injected into the bladder until the patient experiences a desire to void its contents, both conventional roentgenograms and tomograms are taken in suitable projections. The amount of CO_2 injected is generally between 200 and 300 ml. We formerly used oxygen for the intravesical injection too, but changed to carbon dioxide because it is absorbed 30 times more readily than O_2 in plasma (BEST & TAYLOR 1945). This should have eliminated the danger of gas embolism from the intravesical injection. In the tissues, on the other hand, CO_2 is absorbed so rapidly that we have not been able to use it for perivesical injections.

One complication was observed. It occurred in a patient with a large lym-

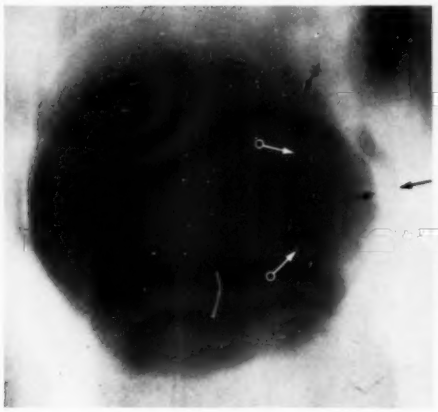


Fig. 3. Case 5. Malignant papilloma infiltrating bladder wall. Tomogram a.p. Sessile tumor (←) situated in left lateral part of bladder; at its base the wall is distinctly thickened (←), no perivesical growth. Bladder wall is not so thick in upper and lower parts of tumor, and is normal above tumor base (↔).

Fig. 4. Case 6. Malignant papilloma. Tomogram a.p. Large irregular tumor in the right lateral part of the bladder. The wall is thickened at the site of the tumor base, but no perivesical growth is evident (←).

phosarcoma which displaced the anterior bladder wall 4 to 5 cm backwards and extended as far as the symphysis pubis. Although the position of the needle in the prevesical space was carefully checked, and no blood escaped through the needle, the patient suddenly lost consciousness during the injection of oxygen. The cause could not be established, but the possibility was not excluded that loss of consciousness was due to gas embolism. The patient soon recovered and showed no ill-effects. In view of this experience we feel that injection of gas into the prevesical space should not be undertaken in patients with large tumors situated in the anterior bladder wall; the gas might then be injected directly into a highly vascular tumor and produce gas embolism.

Material and Results

The series consists of 18 cases, including one normal and 17 of bladder tumors. Pathologic classification conforms to the principles suggested by DUKES & MASINA (1949). Three of the tumors were benign papillomas (Dukes' type 1), three malignant papillomas or differentiated transitional cell carcinomas (Dukes' type 2), eight poorly differentiated carcinomas of the bladder, one a colonic carcinoma which had invaded the bladder, one a sarcomatous

Table

Case report grouped with respect to the roentgenologically determined thickness of the bladder wall

Group	Case	Pathologic diagnosis	Ureteric stenosis	Appearance of tumor
I — No thickening of bladder wall	1	Normal	0	—
	2	Papilloma (Dukes 1)	Not examined	Probably malignant
	3	» »	0	0
	4	» »	+	0
II — Thickening of bladder wall, but no perivesical growth	5	Papilloma (Dukes 2)	0	Probably malignant
	6	» »	+	Malignant
	7	» »	Some stenosis	Probably malignant
	8	Carcinoma	+	Malignant
	9	»	+	Malignant
	10	Carcinoma of colon	Some stenosis	0
III — Perivesical growth	11	Carcinoma	+	Malignant
	12	»	Not examined	Malignant
	13	»	0	Probably malignant
	14	»	0	Probably malignant
	15	»	0	Malignant
	16	»	Not examined	Malignant
	17	Sarcoma	0	Malignant

tumor, and one a lymphosarcoma. The cases have been grouped (see Table) with respect to the roentgenologically determined thickness of the bladder wall at the tumor site. In group I, there was no demonstrable thickening of the wall, in group II, the bladder wall was thickened but no perivesical growth was detectable, and in group III, there was manifest perivesical growth. The bladder wall thickness, at the site of maximum extension of the tumor, was then correlated with the definitive pathologic diagnosis. Since the presence of ureteric stenosis in bladder tumors usually points to malignancy, the table includes the results of urographic examinations as regards possible stenosis. Lastly, the results of evaluation of the general appearance of the tumors, according to FRANKSSON et coll., are given in the table. The number of cases in the three groups was four, six and seven, respectively. The patient with lymphosarcoma was not examined thoroughly due to his loss of consciousness, and the case has therefore been excluded.

Group I, as will be seen from the table, consists of the normal case and the three benign papillomas (Figs 1 and 2). Group II comprises the three malignant papillomas or differentiated transitional cell carcinomas and three less differentiated carcinomas (Figs 3 and 4). Each of the cases in group III had poorly differentiated malignant tumors with verified perivesical growth (Figs 5 to 9).

Three cases in group I, all of those in group II, and 5 in group III were subjected to urographic examinations. In Case 4, referable to group I, there

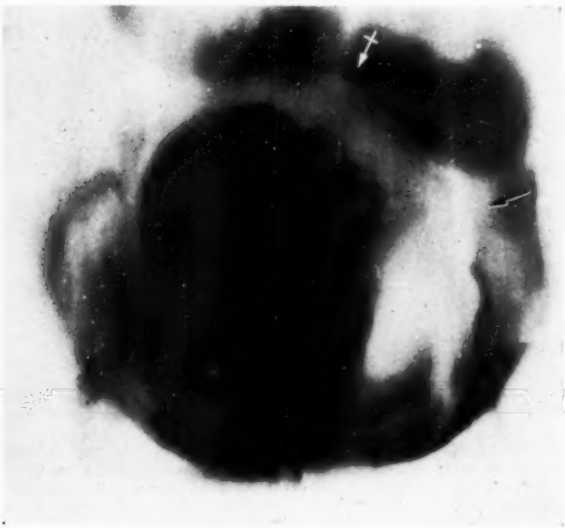


Fig. 5. Case 12. Large carcinoma of left side of bladder. Tomogram a.p. The tumor has grown through the bladder wall in upper left region (←). Gas was insufflated into the large bowel, and the tumor has produced an impression on the sigmoid colon (↔).

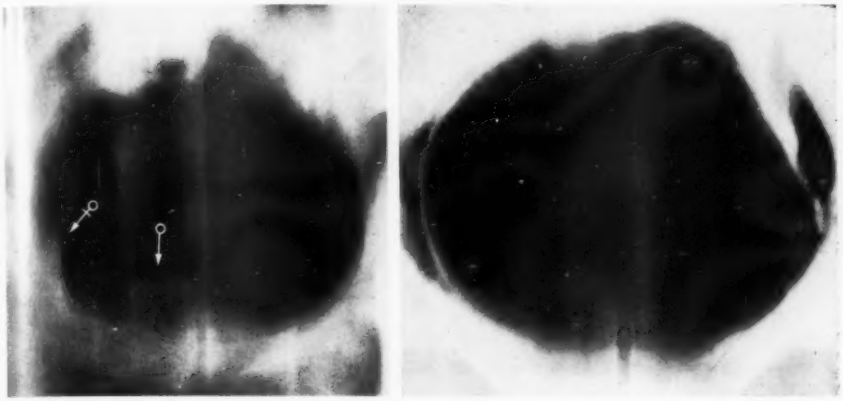
was stenosis of the left ureter but the tumor was situated on the right side. At autopsy the left ureteric stenosis was found to be due to a simple stricture and there was no evidence of tumor.

Five of the 6 cases in group II had varying degrees of ureteric stenosis, but only one of the 5 in group III showed such stenosis.

The general appearance of the tumors was such as to suggest that they might be malignant in five of the six cases in group II, but also in one case referable to group I.

Discussion

Our experience hitherto with the method of perivesical injection of gas for determining the thickness of the bladder wall shows that it is usually possible to judge the thickness both in the anterior, posterior, and superior and lateral walls, but not in the basal parts. In all cases, safe two in group II, there was complete correlation between, on the one hand, the roentgenologically demonstrated thickness of the bladder wall and, on the other, the operative findings and pathologic diagnosis. The two exceptions (Cases 9 and 10) showed perivesical growth that had not been demonstrated at the roentgen examination.



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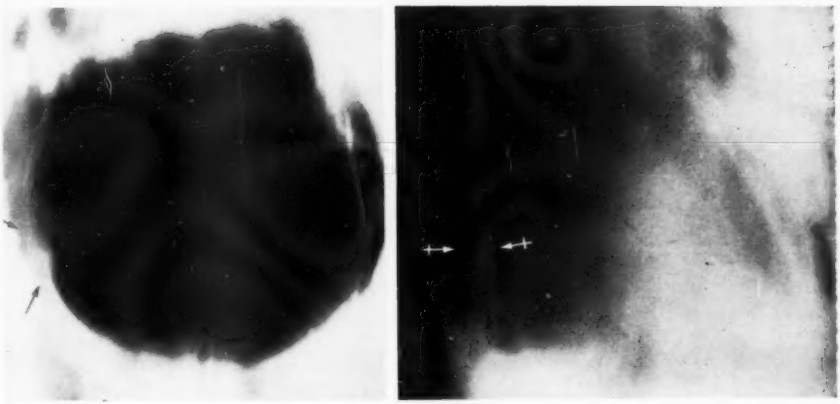

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Fig. 6. Case 13. Two carcinomas of bladder, each about 1 cm in diameter. No tumor was demonstrable at cystography with positive contrast medium. a) At cystography with gas alone and tomography, two tumors were observed, one of them located in the bladder base near the midline (←), the other anteriorly on the right side (↔). The latter tumor had not been detected at cystoscopy. b) With perivesical injection of gas, tomogram a.p. The tomographic section lies behind the tumors. Bladder wall here of normal thickness and no tumor discernible. c) The same as in (b) but with the section through the lateral tumor, which penetrates the bladder wall (←). d) Tomogram lateral. The tumor is growing through the anterior bladder wall into the perivesical fat (↔). The wall above and below it is of normal thickness.

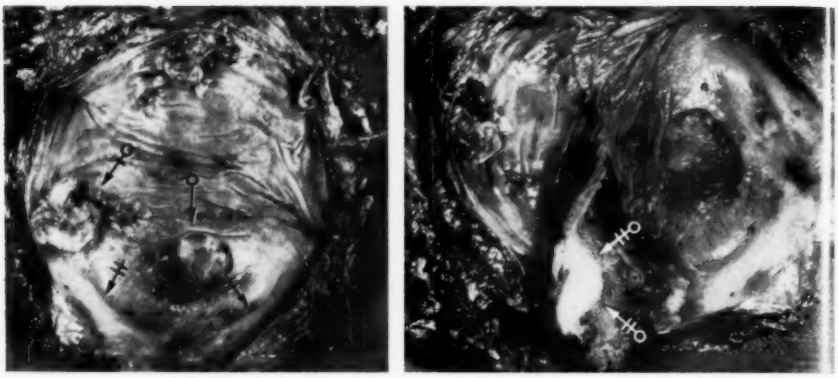

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Fig. 7. Operative specimens of tumors in Case 13. (Cf. fig. 6.) The tumor, situated close to the midline, lies in the bladder base just behind the ureteric ridges (↔). In (b) the lateral tumor has been cut and the wall reflected, disclosing the tumor infiltration into the perivesical fat (↔).

They were, however, among the first examined, and our technique has since improved; they might now possibly be correctly classified. In one of the cases (Case 13) this method enabled us to demonstrate that a tumor no larger than a hazelnut kernel was a carcinoma (Figs 6 and 7).

Ureteric stenosis associated with bladder tumors, as FRANKSSON et coll. have emphasized, often points to malignancy. The absence of stenosis, however, naturally does not rule out a malignant growth. Any ureteric stenosis will naturally depend on the situation of the tumor in relation to the ureter.

SUMMARY

Perivesical insufflation of gas for determination of the bladder wall thickness in tumors of the urinary bladder was carried out in 18 cases. These were grouped with respect to the thickness of the bladder wall and, where present, to the perivesical infiltration. There was close agreement between the roentgenologically determined thickness and the operative findings and pathologic diagnosis.

ZUSAMMENFASSUNG

Perivesikale Gasinsufflation zur Bestimmung der Blasenwanddicke bei Tumoren der Blase wurde in 18 Fällen durchgeführt. Diese wurden mit Hinsicht auf die Dicke der Blasenwand und eventuell vorhandener perivesikaler Infiltration in verschiedene Gruppen eingeteilt. Hierbei fand man enge Übereinstimmung zwischen der röntgenologisch diagnostizierten Blasenwanddicke und den operativen sowie pathologischen Befunden.

Fig. 8. Case 15. Large carcinoma of the right side of the bladder (←). Its growth has extended to the pelvic wall.

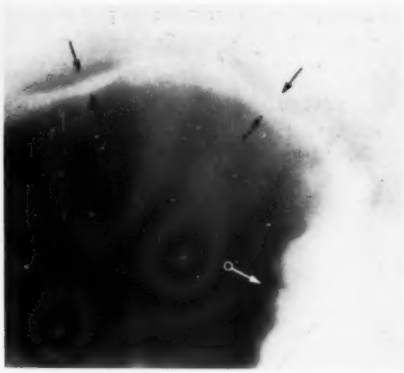

Fig. 9. Case 17. Sarcoma of left lower part of bladder (←). Entire bladder wall somewhat thickened (←). No perivesical gas at site of tumor, which extends to the pelvic wall.

RÉSUMÉ

Les auteurs ont pratiqué dans 18 cas une insufflation périvésicale de gaz pour déterminer l'épaisseur de la paroi vésicale dans des cas de tumeur de la vessie. Ces tumeurs ont été groupées d'après l'épaisseur de la paroi vésicale et d'après la présence ou l'absence d'infiltration périvésicale. Les auteurs ont constaté une bonne concordance entre l'estimation radiographique de cette épaisseur, les constatations opératoires et l'étude anatomo-pathologique.

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LESIONS IN THE DEPTH OF THE BRAIN PRODUCED BY A BEAM OF HIGH ENERGY PROTONS

by

LARS LEKSELL, BÖRJE LARSSON, BENGT ANDERSSON, BROR REXED, PATRICK SOURANDER and WILLIAM MAIR

Beams of light atomic nuclei, such as protons, deuterons or alpha-particles, may be used to destroy small portions of intracranial tissue (TOBIAS et coll. 1954, LARSSON et coll. 1958). The histopathology of radiolesions produced by this technique at different sites in the central nervous system has been described previously (LARSSON et coll. 1959, REXED et coll. 1960).

The present paper describes restricted lesions in the brain produced by cross-fire irradiation. The work forms part of an investigation preliminary to the use of irradiation with high-energy protons in neurosurgery. Goats were used as experimental animals. These animals have rigid skulls which can be conveniently fixed in the same stereotaxic apparatus as constructed for man. The goat's brain is also large enough to enable the volume of necrotized brain tissue to be made relatively small compared to the size of the whole brain. This fact reduces the risk of side-effects, e. g. generalized oedema of the brain.

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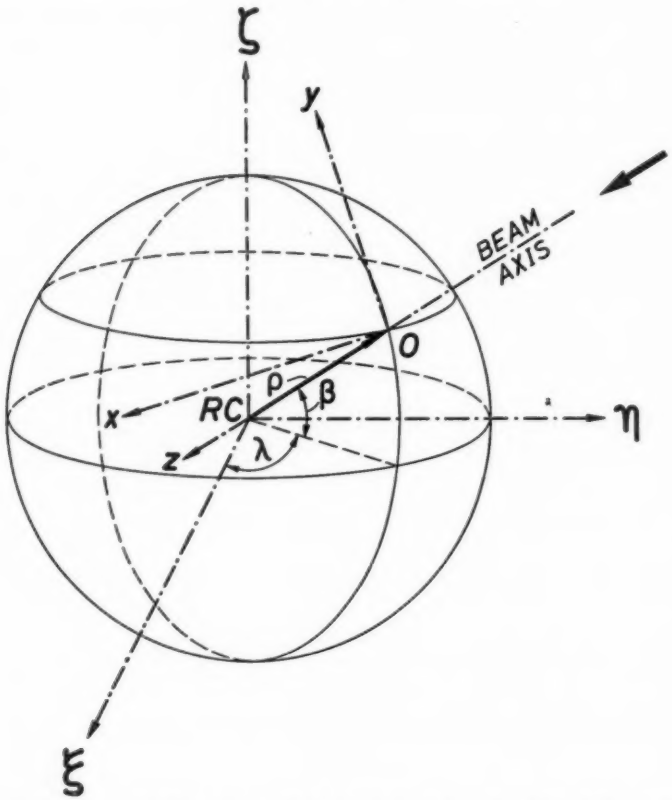

Fig. 1. Coordinate systems for definition of the irradiation parameters given in the table, p. 254. Greek letters refer to the space of the irradiated body, roman letters to the space of the proton beam. The beam passes through the rotation centre *RC* at a depth ϱ, measured along the beam axis. The point *O* at which the axis of the beam meets the surface of the head is localized in relation to the rotation centre *RC* by specifying the latitude β and longitude λ of *O* on a sphere with radius ϱ and centre at *RC*. The rectangular cross-section of the beam measured *a* mm in the *x*-direction and *b* mm in the *y*-direction.

Material and Methods

Radiation technique. The irradiations were performed with a beam of 185 MeV protons from the synchrocyclotron at the Gustaf Werner Institute. The method by which the beam was applied for irradiation has been described by LARSSON et coll. (1959). The doses were measured with an ionization chamber and by activation dosimetry as in the experiments reported by LARSSON (1960). Scattering in the ionization chamber and in air was almost negligible and the beam was collimated to a parallelity of about 1 : 40.

protons scattered in the walls of the apertures contributed only to a very small extent to the dose in the regions of interest in the deeper part of the brain, since most of these scattered protons had a short residual range after having interacted with the material of the walls of the aperture. The contribution to the dose of these protons has been neglected. The cross-section of the beam was almost uniform and measured 2 mm × 10 mm, or 2 mm × 7 mm, as it entered the skull of the animal.

When cross-firing with a parallel beam the dose distribution in the target region, i. e. the region surrounding the rotation centre, is defined by the dose distribution of the single field and by the polar coordinates of the points where the axis of the beam meets the surface of the head (Fig. 1). It is convenient to fix the dose by giving the *ideal centre dose*. This term is used here for the dose which a small piece of tissue would absorb at the rotation centre if substituted for the head of the goat during an otherwise identical irradiation procedure, assuming that the build-up of ionization in the tissue is complete. Since the dose on the beam axis varies little in the first part of the range of penetration (cf. isodose curves for a 1.5 mm beam shown by LARSSON et coll. 1959) the *real centre dose* was nearly equal to the ideal centre dose, provided untoward movements of the skull did not occur during irradiation.

The thin ionization chamber was calibrated in terms of ideal centre dose by measuring the ^{11}C-activity induced in small polystyrene cylinders, 1 mm in diameter, irradiated at the rotation centre. The relation between the specific activity of the polystyrene and the absorbed dose was determined by measuring the ^{11}C-activity of the polystyrene cylinders after irradiation with known doses of protons as measured with the chamber used by FALKMER et coll. (1959). The uncertainty of the figures given for the ideal centre dose was estimated to be 10 per cent.

In order to illustrate the physical conditions of irradiation a distribution of relative dose is given in Fig. 2. The isodose curves were calculated from the measured dose distribution in a single beam and also measured directly in a cylindric water phantom representing the skull of the goat. The measurements were made with photographic film dosimetry. The results obtained by the two methods were in fair agreement. The dose distributions are, however, more strictly defined by the irradiation parameters in the table, p. 254.

In view of the planned clinical applications, where a disc-shaped lesion with a diameter of e. g. 1 cm would be most suitable, it was decided to choose the parameters of the irradiation procedure so as to destroy a selected volume of this shape. It was considered that a dose distribution with its highest gradient at 1 cm diameter would give the greatest probability for a lesion of a suitable and time independent size to be produced (Fig. 7). The doses were chosen so as to induce radionecrosis within a few weeks at points inside the region of high gradient. Outside the region of high gradient there would be, if any, a very much delayed radionecrosis.

Table

Data of irradiation given in accordance with fig. 1. The field size refers to the cross-section of the beam at the surface of the goat's head. The spherical polar coordinates β, λ and ϱ give for each field the position of the point where the beam axis enters the skull in relation to the centre of rotation. The length ϱ of radius vector was between 4 and 7 cm as determined by the contour of the skull. The dose rate was ca 2 krad/min. Between the single irradiations of the multiple field procedures there were intervals of ca 2 min.

Goat No.	Field size $a \times b$ mm²	Number of fields ν	Ideal centre dose krad
1	10 × 2	1	20
2	10 × 2	22	20
3	7 × 2	20	20
4	7 × 2	20	38

Four adult goats were used. One goat was irradiated with a single beam (skin dose = ideal centre dose = 20 krad) directed through the frontal lobe of the right cerebral hemisphere. Two goats were irradiated by cross-fire irradiation with 20 or 22 fields (skin dose ≈ 1 krad, ideal centre dose = 20 krad) in a way which was thought to be suitable for the production of a lesion of the size and shape mentioned above. One goat (No. 4) was cross-fire irradiated with a much higher dose (20 fields, ideal centre dose = 38 krad) in order to study the effects of a dose higher than any which might be used in clinical applications.

Biological methods. One to two hours before operation the goats were given 0.2 g per kilogram bodyweight of chloral hydrate by a stomach tube. Nembutal anaesthesia was induced intravenously and kept at a desired depth for up to 2 hours during the procedure. The goats were intubated and in order to avoid the accumulation of gas a cannula was inserted through the abdominal wall into the dorsal sac of the rumen.

The head of the goat was fixed to the stereotaxic instrument by three drills, 4 mm in diameter, introduced a few millimeters into the skull (Fig. 3). With the exception that bony landmarks were used as reference points, the procedure followed the method described previously (LEKSELL 1951, 1957). When cross-fire irradiation was applied, a point in the right internal capsule was selected as the centre of rotation. All lesions restricted to the depth of the brain were planned so as to appear transverse to the direction of the fibres of the internal capsule.

The animals were killed 1 to 4 months after irradiation by decapitation under Nembutal anaesthesia. Perfusion was performed through the carotids with physiologic saline followed by 5 per cent formol saline. The brain was re-

Angular coordinates		Goat No.
β	λ	
0°	0°	1
8° 0° 8°	−51° −34° −17° 0° +17° +34° +51° −55°.25 −38°.25 −21°.25 −4°.25 +12°.75 +29°.75 +46°.75 −59°.5 −42°.5 −25°.5 −8°.5 + 8°.5 +25°.5 +42°.5 +59°.5	2
0°	−57° −51° −45° −39° −33° −27° −21° −15° −9° −3° +3° +9° +15° +21° +27° +33° +39° +45° +51° +57°	3
8° 8°	−60° −48° −36° −24° −12° 0° +12° +24° +36° +48° +60° −42° −30° −18° −6° +6° +18° +30° +42° +54°	4

moved and fixed for about one week in 5 per cent formol saline. The fixed brains were cut horizontally in slices about 5 mm thick and examined macroscopically. The target region was embedded in celloidin and cut by serial sectioning at about 15 μ. The following staining methods were used: van Gieson, Gros-thionine and Loyez (cf. CULLING 1957). The dimensions of the lesions given refer to the fixed material. No correction factor for shrinkage has been applied.

Experimental results

The neuropathologic observations are given for each animal.

Goat No. 1 — One month after single field irradiation with 20 krad

No symptoms of cerebral injury were noted.

Macroscopic examination. The dura mater was apparently unaffected. Across the convexity of the right frontal lobe and transverse to the length of the hemisphere a brown band about 2 mm wide was seen. The rest of the surface of the brain looked normal.

Microscopic examination. On sections transverse to the path of the beam a lesion was seen extending through the cerebral cortex and dipping about 1 mm into the white matter. The leptomeninges in the path of the beam showed a slight degree of small round cell infiltration. There was no haemorrhage in the membranes. The irradiated cortex was congested and there was frequently exudation of plasma around the vessels. Inside the lesion, which had a breadth close on 2 mm, were degenerated nerve cells, nerve fibres, and glial

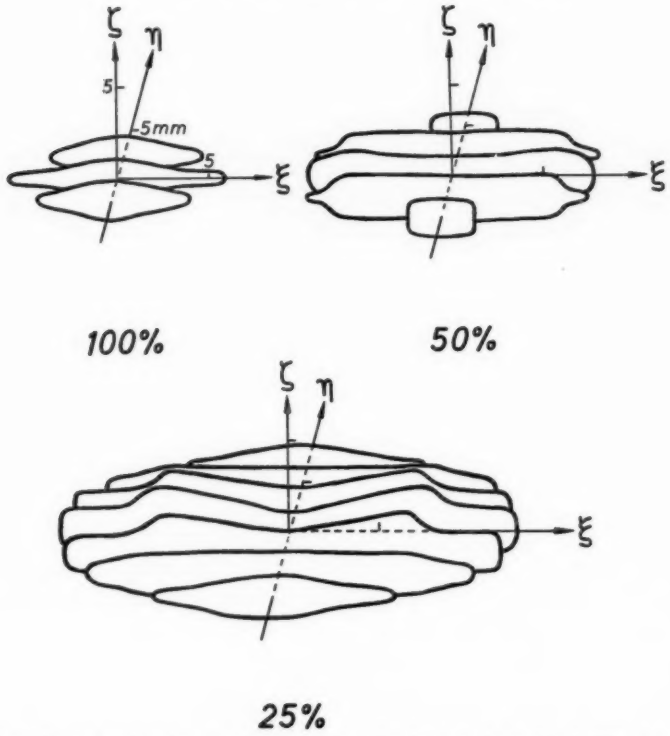

Fig. 2. Three-dimensional isodose curves for the dose distribution of goat No. 2. The doses are given in per cent of the dose at the centre of rotation. The irradiation data are specified in the table, p. 254. For definition of the coordinates see fig. 1.

cells and there were some patches of complete necrosis. A moderate number of macrophages were seen, particularly in the necrosed regions. In and around the necrotic area were small perivascular haemorrhages and dilated thin-walled vessels filled with erythrocytes. A slight proliferation of astrocytes was noted.

The lesion in this goat bore a strong resemblance to the lesions in the brains of rabbits irradiated under similar conditions (Rexed et coll. 1960).

Goat No. 2 — One month after cross-fire irradiation with 20 krad

No symptoms of cerebral injury were noted.

Macroscopic examination. The meninges and the surface of the brain appeared normal. The lesion was localized in the anterior part of the internal capsule.

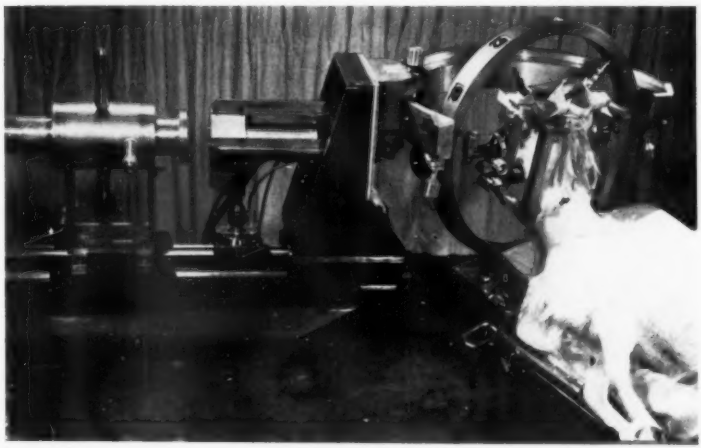

Fig. 3. Goat in position for irradiation, fixed to the stereotaxic instrument. The collimated proton beam enters from the left, leaving the evacuated tube through a thin Mylar window (5 mg/cm²). The ionization chamber (25 mg/cm²), the final aperture and the centre of the semicircular holder of the stereotaxic instrument were aligned with the proton beam by means of an optical bench.

It was roughly lentiform, with a maximum thickness of about 3 mm. The lesion was most extended in the $\xi\eta$-plane (Fig. 1) transverse to the general direction of the fibres of the internal capsule. Medially the lesion entered the head of the caudate nucleus; laterally it entered the putamen (Fig. 4a). The largest diameter of the lesion was in the dorso-ventral direction, i. e. in the direction of the ξ-axis, and measured 13 mm. The maximum width in the horizontal sections was 8 mm.

Microscopic examination. Irregularities of the margin of the lesion were most marked at the medial and lateral edges situated in the grey matter. At the dorsal edge of the lesion prongs of almost completely degenerated tissue jutted into the surrounding white substance, forming a regular pattern (Fig. 4c). This pattern seemed to correspond to the pattern of dose distribution formed by the superimposition of the individual radiation fields in the multiple field irradiation procedure. The dorso-lateral edge of the lesion was very near the bottom of a sulcus; at this point the leptomeninges showed a definite lymphocytic infiltration, and in the neighbouring layers of the cortex there was capillary proliferation. The meninges were elsewhere normal. The central part of the lesion in the white matter was completely necrotic. In the grey matter small perivascular haemorrhages were found. A narrow zone at the margin of the lesion showed degenerating myelin sheaths and axons; there

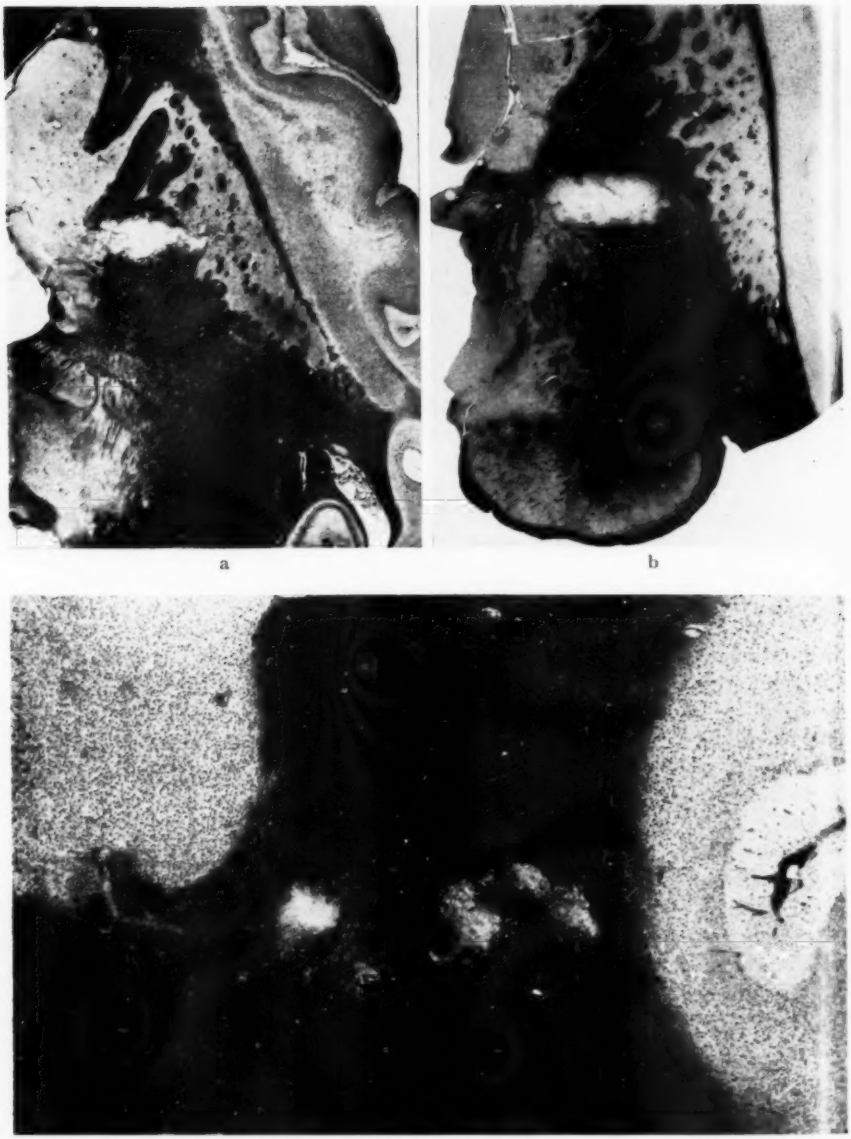

Fig. 4. a) and b). Horizontal sections of the right hemisphere of, respectively, goat No. 2 and No. 3, showing in each a sharply delimited lesion in the internal capsule at, respectively, one month and seven weeks after cross-fire irradiation with 20 krad. Gros-thionin × 3. c) The superior edge of the lesion in goat No. 2 (cf. left view above). Prongs of destroyed tissue jut into the white matter. Round cell infiltration is seen in the leptomeninges in the nearby sulcus. Gros-thionin × 18.

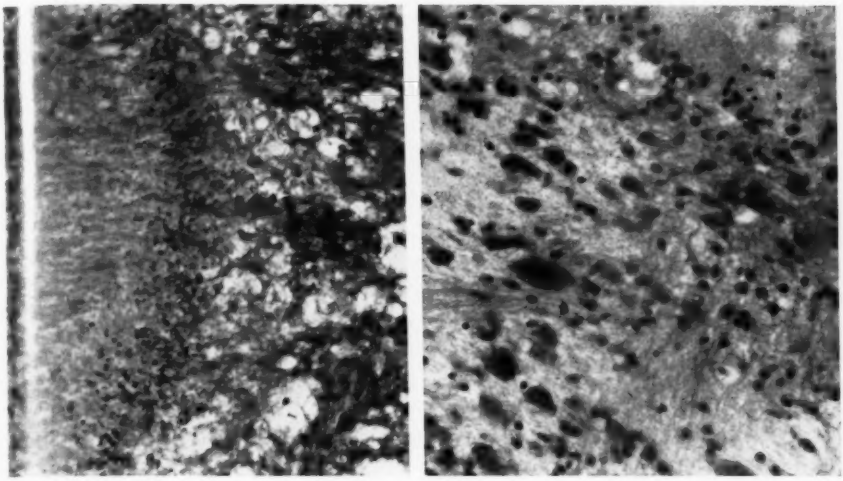

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Fig. 5. a) From the edge of the lesion in goat No. 2 (cf. fig. 4a). A palisade of nuclear debris bounds the necrotic tissue; the adjacent myelin sheaths are swollen and show slight infiltration by round cells. HvG × 120. b) From the edge of the lesion in goat No. 3 (cf. fig. 4b). A layer of nuclear remnants separates the necrotic area from the adjoining grey matter which shows a mild degree of round cell infiltration and well preserved nerve cells. HvG × 200.

was also slight cellular proliferation in this zone. A palisade of disintegrating nuclei, several layers deep, bounded the necrotic lesion (Fig. 5a). Where the lesion extended close to the ventricle wall the ependyma was undamaged. Outside the lesion there were no signs of pathologic processes.

Goat No. 3 — Seven weeks after cross-fire irradiation with 20 krad

No symptoms of cerebral injury were noted.

Macroscopic examination. The meninges showed no pathologic changes. The exterior of both hemispheres looked normal and there were no signs of oedema or haemorrhage. A lesion of greyish colour was found in the depth of the right hemisphere. It was situated in the posterior limb of the internal capsule between the thalamus and the globus pallidus just behind the genu (Fig. 4b). No haemorrhages were observed in the lesion or its surroundings. The lesion was most extended in the $\xi\eta$-plane transverse to the general direction of the fibres of the internal capsule. The longest diameter of the lesion was in the dorso-ventral direction, i. e. the direction of the ξ-axis and measured 13 to 16 mm. The maximum width of the lesion in the horizontal sections was 7 to 10 mm. The maximum thickness in the antero-posterior direction was about 3 mm.

Microscopic examination. The picture in detail corresponded closely to that described in goat No. 2. Within the white matter the lesion was sharply limited. The myelin sheaths, axons and glial cells were completely destroyed in the main part of the lesion. The capillaries were also destroyed and around them were shadows of erythrocytes and plasma exudate. There were no large haemorrhages inside the lesion or around it. At the margin of the lesion and immediately inside it were a few small, thin-walled and distended vessels filled with closely packed blood corpuscles. In the vicinity of these vessels a small number of macrophages containing particles of myelin were present. At one end of the lesion a seemingly well preserved larger vessel surrounded by macrophages crossed the degenerated zone. The lesion was delimited by a mass of nuclear remnants and a number of cells with small pycnotic nuclei and scanty cytoplasm.

A narrow zone, 200 to 400 microns broad, surrounded the main lesion and showed degenerating axons and myelin sheaths. In this zone there was a slight interstitial cellular proliferation and some lymphocytes around the vessels (Fig. 5b). The tissue further away from the lesion appeared undamaged.

Goat No. 4 — Four months after cross-fire irradiation with 38 krad

The animal became blind in its left eye. When walking it tended to deviate to the right.

Macroscopic examination. The meninges and the exterior of the brain looked normal. A fairly large lesion was seen in the depth of the right hemisphere. The lesion was mainly localized to the genu and the posterior limb of the internal capsule, but encroached medially on the thalamus and laterally on the lentiform nucleus. Its form was irregular in the horizontal section but the main axis was transverse to the general direction of the fibres of the internal capsule (Fig. 6a). The lesion had a greyish-yellow centre and a fairly large reddish-brown border. In the horizontal section the dimensions of the lesion were 4 to 5 mm by 10 mm; in the dorso-ventral direction its length was 15 to 20 mm. There was marked swelling of the right hemisphere and the midline structures were displaced towards the left.

Microscopic examination. A large part of the lesion was necrotic. The tissue around the necrotic area in some places contained wide, thin-walled newly formed vessels and was densely infiltrated with inflammatory cells and macrophages (Fig. 6b). Throughout the area of cellular reaction were spaces containing fluid and macrophages and traversing the spaces were nerve fibres and blood vessels. Outside this zone there was a region where the vessels were surrounded by numerous lymphocytes and mononuclear cells; only minimal haemorrhages were observed in this area. The affected region surrounding the necrosis was at least the size of the necrotic area itself. Other parts of the brain showed no pathologic changes.

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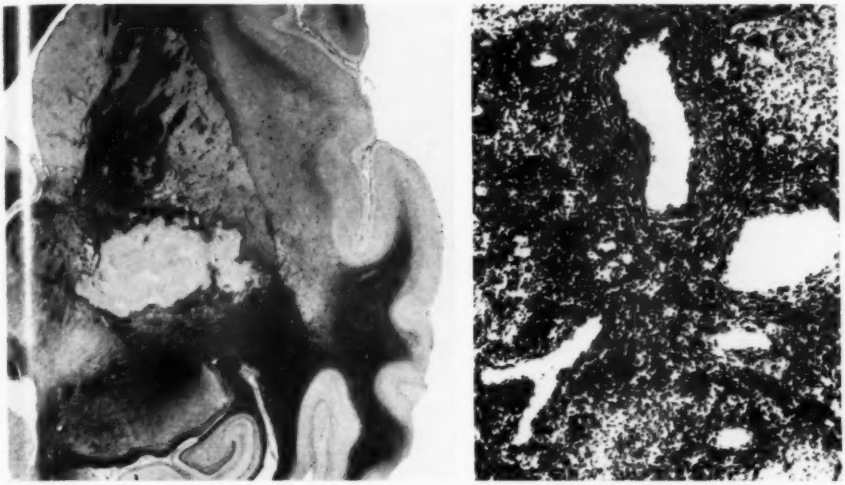

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Fig. 6. a) Horizontal section of the right hemisphere of goat No 4, showing a fairly large necrotic area in the thalamus, posterior limb of the internal capsule, and the lentiform nucleus. Loyez × 3. b) The necrotic tissue in goat No 4 (cf. fig. 6a) bounded by numerous newly formed capillaries surrounded by small round cells. Collections of macrophages lie between these vessels. HvG × 75.

Discussion

The aim of the investigation was to study the features of a restricted radiolesion in the depth of the brain produced by cross-fire irradiation with a narrow beam of high energy protons. The results show that by careful selection of doses and dose distributions, well circumscribed intracerebral lesions of appropriate size and shape can be produced (goats Nos 2 and 3). This statement is valid only for the earlier stages of the radiolesion, as only relatively short survival periods are considered.

A suitable dose for the production of a discrete lesion is 20 krad. Such a dose causes circumscribed destruction of the nervous tissue, small perivascular haemorrhages and slight cellular proliferation at the periphery of the lesion. The lesion in goat No. 1, produced by 20 krad using a single field, was essentially similar to the lesions effected in rabbits by a similar technique and described by Larsson et coll. (1959) and Rexed et coll. (1960).

The circumscribed lesions in goats Nos 2 and 3 following cross-fire irradiation showed similar pathologic changes. A striking feature of these two lesions was the paucity of cellular reaction at the periphery of the lesion.

In goat No. 4 a dose of about 40 krad produced a very different lesion. The volume of necrotic tissue was large and there was a very intense tissue

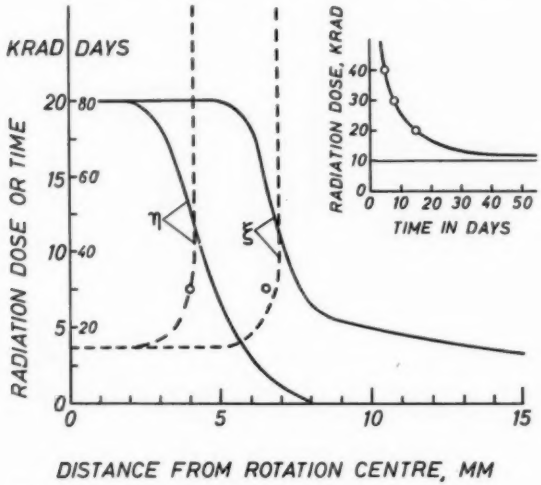

Fig. 7. The calculated dose (————) and the time after irradiation at which necrosis was estimated to appear (– – – – –) along the ξ —and η -axes in the target region of the brain of goat No. 2. The time curves were constructed from the dose curves and from the data in the small diagram, showing the time at which necrosis has been found to appear in the brain of the rat after irradiation with different doses of protons (LARSSON 1960). The dimensions of the lesion in the brain of goat No. 2, measured 30 days after irradiation, are indicated.

reaction surrounding it. The inflammatory reaction was chronic in type: dense lymphocytic and histiocytic proliferation and formation of new capillaries. The affected region surrounding the necrotic area was broad while after irradiation with 20 krad there was little reaction around the necrotic area. The irradiated hemisphere in goat No 4 was markedly swollen. Thus a radical increase of the dose above 20 krad, considered the optimum dose, induced wide-spread tissue reaction as well as the desired destruction of tissue at the centre of rotation. This observation stresses the importance of selecting the dose carefully when planning any operative procedure.

Of special interest is the relation between the size and shape of the lesion and the dose distribution. Some observations suggest that small irregularities of the dose distribution at the margin of the lesion are reflected in the shape of the lesion (Fig. 4c). If this is so, it should be possible to destroy tissue volumes of almost any shape in the brain. It should be stressed, however, that the size and shape of the lesion are dependent on the survival time. The situation is exemplified in Fig. 7. The solid lines in the larger diagram show the dose as a function of the radius along the ξ- and η-axes (for definition see Fig. 1). The curve in the small diagram shows the approximate relationship between

t time for the necrosis to appear after irradiation as a function of the radiation dose. It is based on earlier experiments in rats (LARSSON 1960). For the purpose of discussion the latter relation is assumed to be valid also for the lesions following cross-fire irradiation of the brain of the goat. Under these conditions the time at which the tissue at different radii will undergo necrosis would follow the dotted curves in the larger diagram (Fig. 7). These curves show sharp bends in the region of the sharpest gradient of the dose distribution. Having passed this region the margin of the lesion will advance slowly and in an asymptotic way approach a contour outside which no necrosis will ever appear. Of course the diagram gives only a general illustration of the process of growth of the lesion. It does not consider varying biologic conditions.

When deciding on doses and dose distributions earlier data on the relation between the dose and the time required for the radio-necrosis to occur were used. Despite the fact that these data were obtained in experiments with rabbits (LARSSON et coll. 1959, REXED et coll. 1960) and rats (LARSSON 1960) the estimations were found to hold fairly well also for the goat.

The results presented show that by means of proton irradiation it is possible to destroy small restricted areas deep in the brain without damaging surrounding brain tissue. The early stages of such lesions may be used to advantage in physiologic experimentation. The extent to which the method may be applied to neurosurgery in man will depend on many factors. Of main interest are the late effects of high energy protons on the brain now being investigated in long term experiments.

Acknowledgements

The authors wish to thank K. W. Ståhl for invaluable technical help, M. Johansson for the histologic preparations and J. A. Mills for the photomicrographs. The investigation was supported by the Knut and Alice Wallenberg Foundation and the Swedish Medical Research Council; part of the technical work was assisted by The Swedish Technical Research Council and the Office of Scientific Research of the Air Research and Development Command, United States Air Force, through its European Office, under Contract No. AF 61 (052)—183.

SUMMARY

Restricted lesions were produced in the depth of the goat's brain by means of cross-fire irradiation with a narrow beam of high energy protons. The radiosurgical technique and the histopathology of the lesions are described. It was possible to produce circumscribed cerebral lesions of a type well suited for physiologic experimentation without damaging surrounding nervous tissue. The method may also be applied to neurosurgery in man.

ZUSAMMENFASSUNG

Mittels der Kreuzfeuerbestrahlung mit einem schmalen Strahl von Hochenergieprotonen wurden in der Tiefe des Gehirns der Ziege begrenzte Läsionen erzeugt. Es wird die strahlenchirurgische Technik und Histopathologie der Schäden beschrieben. Es war möglich,

zirkumskripte cerebrale Läsionen von der Art zu erzeugen, die physiologische Experimente ohne Gefahr einer Schädigung des umgebenden Gewebes gestatten. Die Methode kann auch für neurochirurgische Zwecke am Menschen zur Anwendung kommen.

RÉSUMÉ

Des lésions limitées ont été produites dans la profondeur du cerveau de chèvres au moyen d'irradiation à feux-croisés par un faisceau étroit de protons de haute énergie. La technique radio-chirurgicale et l'histopathologie des lésions sont décrites. Il a été possible de produire des lésions cérébrales circonscrites d'un type convenant bien à l'expérimentation physiologique, sans endommager le tissu nerveux environnant. Cette méthode peut aussi être appliquée à la neurochirurgie chez l'homme.

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FROM THE ROENTGEN INSTITUTE (DIRECTOR: PROF. G. G. PALMIERI) OF BOLOGNA UNIVERSITY, ITALY

IMPRESSION OF THE LEFT ATRIUM ON THE SUPERIOR VENA CAVA AND SINUS OF THE VENAE CAVAE IN MITRAL DISEASE

by

G. F. GARUSI

A great many roentgenologic investigations of mitral disease based upon angiocardiography have been reported during the last decade (GRISHMAN et coll. 1944, DOTTER & STEINBERG 1951, ACTIS-DATO et coll. 1952, ZINSSER et coll. 1952, DE GIULI 1954, ARVIDSSON 1958). These studies have been stimulated primarily by considerations of treatment made possible by new surgical techniques. The data obtained from the angiocardiographic examination are essential both to the cardiologist and the surgeon in indicating the suitability of a case for operation as well as the technique to be employed (MCAFEE et coll. 1956, MOUQUIN et coll. 1956).

The angiocardiographic appearances of the left atrium in mitral disease afford exact information regarding the type and extent of the valvular defect, the predominance of stenosis (or insufficiency in the case of combined valvular disease) as well as the presence of other cardiopathies (BJÖRCK et coll. 1953).

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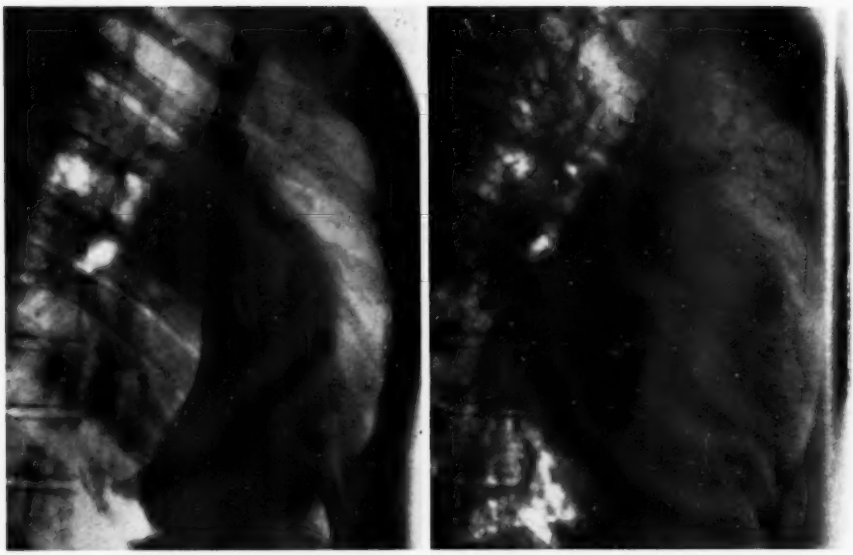

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Fig. 1. Case 1. Slight mitral stenosis and insufficiency with gross dilatation of pulmonary artery. A.p. diameter of thorax 14 cm. a) Superior vena cava, right atrium and auricle, right ventricle and main trunk of pulmonary artery contrast filled. Slight impression of large radius by left atrium on sinus of venae cavae. A second impression due to the right branch of the pulmonary artery on the superior vena cava. b) Left atrium of moderate size (120 cc).

The purpose of this brief report is to demonstrate the topographic relationship of the left atrium in cases of mitral disease, with special reference to the superior vena cava and the sinus of the venae cavae. The findings have been collected from routine angiocardiographic examinations. Serial films in two projections were obtained in all cases.

Angiocardiographic appearances

The left atrium is on both sides held down by the pulmonary veins, and can consequently expand only transversely, or in the sagittal plane. This has been recognized from the earliest days of roentgenology and is well demonstrated by PALMIERI's tridimensional plastic casts of the heart.

The direction of the enlargement of the left atrium is dependent upon the type of thorax. In the asthenic, or the flat, type of chest, the enlargement of the left atrium will occur mostly in a transverse direction. The orientation of the heart in the thorax (WALMSLEY 1958) and the size of the other cardiac

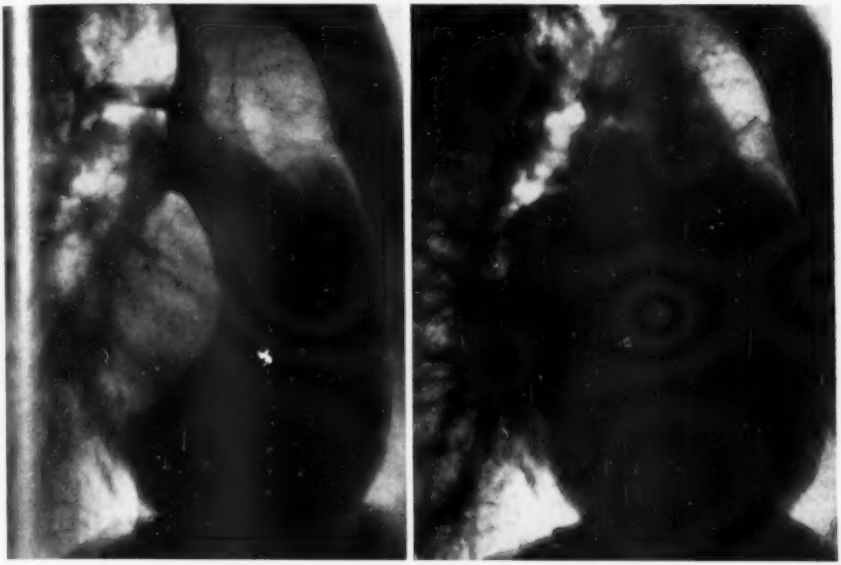

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Fig. 2. Case 3. Mitral stenosis and insufficiency with tricuspid stenosis. A.p. diameter of thorax 13.5 cm. a) Reflux of contrast medium into azygos vein, right superior intercostal vein and inferior vena cava. Superior vena cava, and right atrium, and its auricle are all dilated. Impression of small radius on superior vena cava and sinus of the venae cavae. b) Left atrium moderately increased in size sagittally and longitudinally (170 cc). Right cardiac chambers still remarkably well filled.

chambers are also among the factors which may influence the direction of the atrial expansion.

The increase in the transverse diameter is generally evident in the frontal projection as a displacement of the lateral margin on the left atrium towards the right and the formation of a double outline on the right side of the heart. A widening of the bifurcation of the trachea with upward displacement of the main bronchi, particularly the left, will be observed. Furthermore, the oesophagus, if outlined by means of a barium swallow, will show a regular defect or impression along the left border of its lower third.

The increase in the sagittal diameter is indicated in the lateral projection by a posterior displacement of the oesophagus; anteriorly the left atrium presses to a varying degree on the lower part of the superior vena cava and the posterior wall of the superior half of the right atrium, corresponding to the so-called sinus of the venae cavae.

Table

Case material and findings

Case Cardiopathy	Characteristics of impression			Size* of left atrium (cc)	Reflux into azygos vein	Reflux into inferior vena cava	Sagitta diamete of thora (cm)
	Size	Radius	Seat				
1 Slight mitral stenosis + insufficiency with pulmonary stasis	+	Large	Venae cavae sinus	120	—	—	14
2 Moderate mitral defect with adhesive pericarditis	++	Large	Venae cavae sinus	165	+	+	20
3 Mitral stenosis + insufficiency with tricuspid stenosis	+++	Small	Superior vena cava, venae cavae sinus	170	+	+	13.5
4 Mitral stenosis	++	Large	Superior vena cava venae cavae sinus	210	+	—	20.5
5 Mitral stenosis + insufficiency	+++	Small	Superior vena cava. venae cavae sinus	240	+	+	14.5
6 Pure mitral stenosis	++++	Small	Venae cavae sinus, superior vena cava	315	—	+	14.5
7 Mitral stenosis	+++	Moderate	Venae cavae sinus, superior vena cava	335	—	+	15
8 Marked mitral stenosis with pulmonary stasis and probable aortic insufficiency	++	Moderate	Venae cavae sinus, superior vena cava	380	+	+	17.5
9 Mitral stenosis with aortic insufficiency	++++	Small	Superior vena cava, venae cavae sinus	445	+	+	14.5

* Left atrium sizes have been computed according to the ARVIDSSON formula.

Material

Our material consists of 9 cases of mitral disease, some being associated with other cardiac lesions.

As can be seen from the figures, the lower part of the superior vena cava and the upper part of the sinus of the venae cavae to a varying degree appear indented from behind by the enlarged left atrium. The left atrium is shown in the late serial films to be well filled and so providing beyond doubt the topographic relation.

The case material and the salient features of the films are assembled in the above Table. It would appear that the size of the impression caused by

a b

Fig. 3. Case 6. Pure mitral stenosis. A.p. diameter of thorax 14.5 cm. a) Impression of small radius on superior vena cava and sinus of the venae cavae. Obvious reflex into inferior vena cava. b) Left atrium of large size (315 cc). Marked increase in sagittal and longitudinal diameters in relation to transverse diameter.

the left atrium is dependent, on the one hand, on the degree of enlargement of the left atrium and its sagittal diameter and, on the other hand, on the sagittal diameter of the thorax. The type of the left atrial impression varies with the condition, that is the impression may be one of large radius, as in Cases 1, 2 and 4 (cf. Fig. 1) or one of medium or small radius, as in Cases 3, 5, 6, 7 and 9 (cf. Figs 2, 3, and 5).

It appears that the variation may be related to the sagittal (anteroposterior) diameter, the longitudinal (supero-inferior) diameter or the transverse (lateral) diameter of the dilated left atrium; it may also bear a relationship to the ratio between the sagittal diameter of the thorax and the sagittal diameter of the left atrium.

The impression of the left atrium is in some cases found only on the upper part of the sinus of the venae cavae (Cases 1 and 2) while in others both on the posterior part of the venae cavae sinus and the posterior wall of the lower part of the superior vena cava.

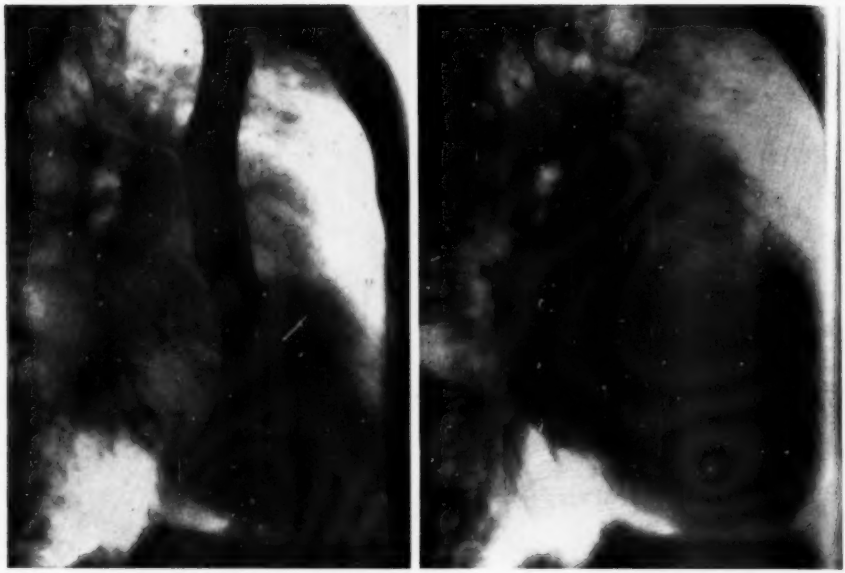

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Fig. 4. Case 8. Marked mitral stenosis with pulmonary stasis; probable aortic insufficiency. A.p. diameter of thorax 17.5 cm. a) Impression of moderate radius on the superior vena cava and sinus of the venae cavae. Small reflux into azygos vein and inferior vena cava. b) Left atrium although very large (380 cc) causes only a slight impression, probably due to the very large a.p. diameter of thorax; left ventricle and ascending aorta much increased in size.

A further feature which we feel deserves mention is a reflux into the arch of the azygos vein, present in varying degrees in 6 of the 9 cases. This sign, which we have observed in other heart conditions, might in these cases of mitral disease be interpreted as being caused by a decreased blood flow in the superior vena cava; this may be due in part to the compression by the enlarged left atrium on the subazygotic tract of the superior vena cava, but mostly to the higher right endo-atrial pressure further increased by the injection of contrast medium. Reflux may also be observed in the inferior vena cava, as in Cases 2, 3, 5, 6, 7, 8 and 9 (cf. Figs 2, 3, 4, 5). The amount of this reflux is variable and it is not proportional either to the size of the impression of the left atrium or to the reflux into the azygos vein; it might perhaps depend on whether the orientation of the axis represented by the two venae cavae is perpendicular.

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Fig. 5. Case 9. Mitral stenosis with aortic insufficiency. A.p. diameter of thorax 14.5 cm. a) Large impression on superior vena cava, somewhat smaller on sinus of the venae cavae. Obvious reflux into inferior vena cava; some reflux into azygos vein. Marked dilatation of trunk of pulmonary artery. b) Enlargement of left atrium (445 cc) due to increase in its sagittal and particularly in its longitudinal diameter. Ascending aorta much dilated.

SUMMARY

An impression on the superior vena cava and the sinus of the venae cavae caused by the enlarged left atrium in cases of mitral disease is described. It is shown to bear a definite relationship to the degree and type of atrial enlargement as well as to the sagittal diameter of the thorax.

ZUSAMMENFASSUNG

Eine Impression der V. cava sup. und des Sinus beider V. cavae, hervorgerufen durch den vergrösserten linken Vorhof bei Fällen von Mitralklappenerkrankung, wird beschrieben. Es wird gezeigt, dass eine bestimmte Beziehung dieser Impression zum Grad und Typ der Vorhofsvergrösserung wie auch zum sagittalen Diameter des Thorax besteht.

RÉSUMÉ

L'auteur décrit une empreinte sur la veine cave supérieure et sur le sinus des veines caves, due à l'augmentation de volume de l'oreillette gauche, dans des cas de maladie mitrale.

Il montre que les dimensions de cette empreinte sont nettement en rapport avec le degré et le type de l'augmentation de volume de l'oreillette et avec le diamètre sagittal du thorax.

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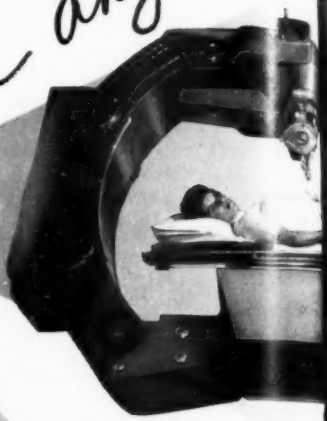

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FROM THE DEPARTMENT OF RADIOTHERAPEUTICS (DIRECTOR: PROF. J. S. MITCHELL), UNIVERSITY OF CAMBRIDGE, ENGLAND, AND THE DEPARTMENT OF PATHOLOGY, NORTHWESTERN UNIVERSITY MEDICAL SCHOOL, CHICAGO, AND ARGONNE NATIONAL LABORATORY, LEMONT, ILLINOIS, U.S.A.

RADIOGRAPHIC APPEARANCES OF BONE LESIONS IN RATS EXPOSED TO LOCAL EXTERNAL IRRADIATION FROM GAMMA RAYS

by

D. B. CATER, R. BASERGA and H. LISCO

Complications arising from damage to bone have often in the past been a limiting factor in radiotherapy of certain types of lesions with conventional roentgen rays, and radiation-induced changes in bone have been described in many publications (EWING 1926, VAUGHAN 1956). These changes occurred not because of a greater sensitivity of bone to ionizing radiations, but because the absorption of roentgen rays of 220 kV is about 2 to 3 times greater in bone than in surrounding or overlying soft tissues (SPIERS 1949). However, complications of this kind can now be largely avoided by the use of more energetic roentgen rays or gamma rays.

Among the important complicating sequelae arising from radiation damage to bones are: (1) Stunting of bone growth in children (NEUHAUSER et coll. 1952); (2) Necrosis of bone with or without fractures (SLAUGHTER 1942, KOK 1953, STEPHENSON et coll. 1956); (3) Very rarely, malignant tumours of bone (CAHAN et coll. 1948, CRUZ et coll. 1957; SABANAS et coll. 1956). The evolution of radiation-induced changes in the bones of patients following radiotherapy has not been studied systematically, although GRATZEK et coll. (1945) followed the appearance of the bones in the field of irradiation in

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568 patients who had undergone radiotherapy for malignant tumours of the genitalia, by performing annual roentgen examinations of the pelvis following radiotherapy. These authors found that 3.2 per cent of the patients developed changes in the irradiated bones such as areas of rarefaction or sclerosis and multiple fractures; these developed from 5 to 22 months after exposure and they occurred more frequently with the use of a more intensive type of radiation therapy. WOODARD and COLEY (1947) studied the effects of roentgen irradiation on regeneration and growth of normal bone adjacent to bone lesions in 22 patients who had been treated for a variety of benign and malignant skeletal lesions and in whom the period of observation following irradiation ranged from one to fourteen years. The authors found no evidence of damage that could be detected roentgenologically in three adults and one child, who had received bone doses from 1 710 to 3 000 roentgens, whereas higher doses (3 470 to 7 790 r) produced variable degrees of impairment, ranging from abnormalities in texture and loss of density to complete devitalization of bone in 11 adults and 7 children. Some of the minor abnormalities which were seen at the intermediate dosages (3 470 to 4 290 r) were transient while all others were permanent.

The radiologic appearance of the bones of patients, containing variable amounts of injected or ingested radioactive materials in the skeleton, has been studied in great detail in recent years (AUB et coll. 1952; LOONEY et coll. 1955 and LOONEY 1958). The radiologic appearance of the bones of these patients changed very slowly, and detectable lesions did not occur, as a rule, until many years after ingestion, and not until impairment of the nutrition and the anatomical structure of these bones had reached considerable proportions. Similar observations have been made on a variety of experimental animals with radioactive materials such as strontium, radium and plutonium (FINKEL & BISKIS 1959, RUBIN et coll. 1959).

A systematic study of the radiologic appearance of bones of experimental animals following external irradiation has not been made, to our knowledge, and we therefore wish to record observations which were made in the course of an investigation of the delayed effects of external gamma irradiation on the bones of growing rats. In this experiment, we had the opportunity to examine many diagnostic roentgen films of irradiated bones; these had been taken at regular intervals in an attempt to follow the development of bone lesions from the time of irradiation until the end of the experiment 2 years later. The principal results of this experiment have been reported recently (CATER et coll. 1959).

Material and Methods. Both knee joints of 136 female Wistar rats (60 days old) were irradiated with a single dose of 3 000 r. The field of irradiation included about 1 cm of both the femoral and tibial shafts. The irradiation

was given with a Ir^{192} teletherapy unit emitting primary gamma rays with a mean energy of 0.38 MeV (half-value layer 8.1 mm Cu). Calculations based on the data of SPIERS (1949) showed that the dose to the bone substance proper from these gamma rays was not more than 10 per cent greater than the dose to the surrounding soft tissues. The 136 irradiated rats were randomized in 4 groups A, B, C and D, while 34 littermates were placed in the non-irradiated control groups E, F, G and H. Eighty days after irradiation, groups A and E received daily injections of growth hormone for 10 weeks amounting to a total of 20.58 mg per rat, groups B and F received daily injections of thyroxine, also for 10 weeks, amounting to a total of 1.98 mg per rat; groups C and G received a 10 weeks' course of growth hormone injections followed by thyroxine injections for another 10 weeks; groups D and H were given saline injections.

Diagnostic roentgenograms were obtained of the irradiated limbs of all surviving animals at 185, 280 and 386 days after irradiation; a final roentgen film was taken at the time of autopsy. Roentgen films were also available on a number of animals that died between the 50th and the 185th day, and the last animals were killed 755 days after the beginning of the experiment. Thus, diagnostic roentgen films were available covering a span of 2 years. Histopathologic examinations were made on most of the irradiated and on control bones, as well as on the viscera and endocrine organs.

Results

The results of the experiment may be briefly summarized as follows:

A single dose of 3 000 roentgen of gamma radiation from a Ir^{192} teletherapy source applied to both knee joints, (equivalent to 4 major epiphyses and 4 cm of bone shaft) of growing female rats produced osteosarcomata in 34 out of 116 rats (29.3 per cent), with a mean induction time of 488 ± 44 days, and fibrosarcomata of the soft tissues in 50 out of 116 animals (43 per cent) with a mean induction time of 453 ± 36 days. Ten animals developed skin carcinomata, and 12 had mammary cancers. Treatment of the irradiated animals with growth hormone somewhat increased the total incidence of the bone sarcomata, while thyroxine significantly shortened the mean induction time of radiation-induced osteosarcomata. The incidence and induction time of the fibrosarcomata and of the other types of tumours was not affected by the hormone treatments.

Since the treatment with either growth hormone or thyroxine did not have any perceptible influence on the radiographic or histopathologic appearance of the irradiated bones, all irradiated animals will be considered as a single group in the following discussion of the findings on the diagnostic roentgen films.

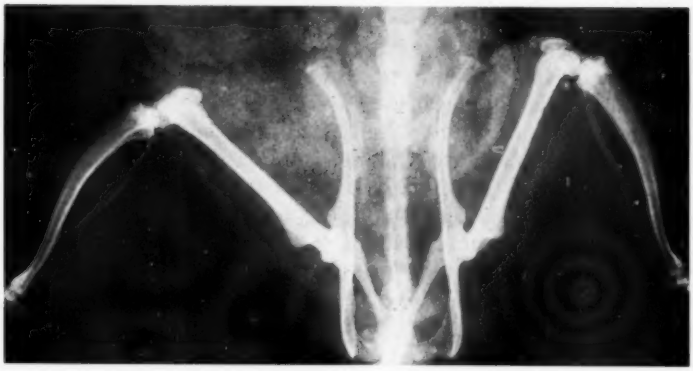


Fig. 1. Roentgenogram of a 16-month-old non-irradiated contro rat.

Fig. 2. *Central* view shows roentgenogram of a rat 185 days after irradiation. Mottling of the left femur. *Lateral* views show right and left knee joints of the same rat 386 days after irradiation. Single punched-out lesion in the left femur.

For comparison with the irradiated animals, roentgenograms of a control rat are shown in Figs 1 and 8.

Stunting of growth. This was the earliest detectable change and was observed in all animals. It was found that the irradiated bones had ceased to grow until about the 100th day post-irradiation and that growth commenced again thereafter. The degree of shortening of the legs averaged 7.2 mm for the femora and 6.5 mm for the 2 tibiae, as determined by measuring the length of the bones from the roentgenograms. The shortening is clearly visible on most of the figures to follow (i.e. compare the length of the femoral shafts in Fig. 1 with Fig. 2).

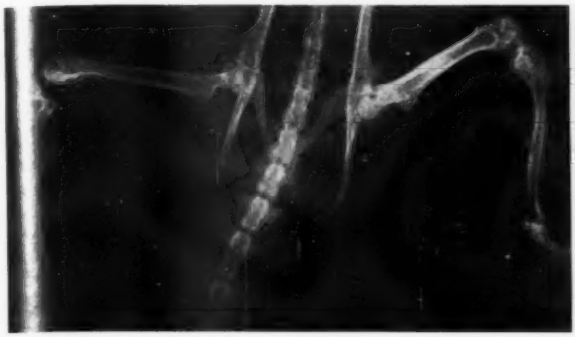


Fig. 3. Roentgenogram of rat 185 days after irradiation. Severe damage of the lower epiphysis of right femur and displacement of patella. Less prominent lesions in left leg.

Fig. 4. Roentgenogram 185 days after irradiation. Atrophy of left femur.

Early and often transient bone changes. Small patches and streaks of rarefaction of bone, especially in the cortex of the metaphyses, were observed between the 50th and 100th day after irradiation (see Fig. 9), and increased in severity up to the 185th day after exposure in the animals that had died before that day. On the 185th day the first diagnostic roentgenologic survey of the knee joints of all surviving irradiated animals showed the following:

There were moderately severe irregularities in the calcification of the bones of a large proportion of the animals and these were characterised by streaks and patches of demineralization (radiolucency) in the cortex; these were often found side by side with areas of increased density. A few animals showed distinct punched-out osteolytic foci, and these were usually located either in the epiphysis or in the upper part of the metaphysis in close proximity to the epiphyseal plate (Fig. 2). The contours of the shafts of the bones were quite irregular and somewhat deformed in some animals, whereas others showed relatively little change. Thus, the appearance of the bones at this time varied considerably from animal to animal and often even in the same animal (Fig. 3). However, all of the animals that were examined at this time showed some degree of abnormality. Irregular calcification of the left femur and tibia and loss of fine structure, especially of the head of the tibia are seen in Fig. 3. The right femur shows partial destruction of the epiphysis and a wide separation of the heads of the femur and tibia; this may have been caused by distention of the joint with fluid or exudate. The patella is partially destroyed and displaced. (This rat developed a spindle cell sarcoma with pleomorphic cells in the region of the right knee, first palpable at 239 days.)

More severe and persistent bone changes. Destruction of bone such as illustrated in the right femur in Fig. 3 was more extensive in some other animals in whom

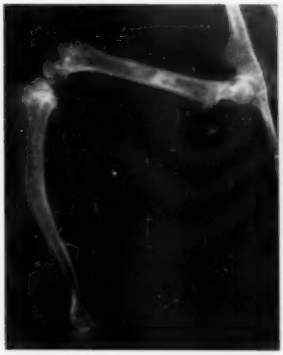


Fig. 5. Roentgenogram of rat 186 days after irradiation. The bar across the shaft of femur should be observed.

Fig. 6. Photomicrograph of lesion in fig. 5, devitalized old spongiosa in mid-shaft of femur. Hematoxylin and eosin. × 85.

Fig. 7. Roentgenogram of rat 280 days after irradiation. Detachment of patella and severe damage of lower epiphysis of right femur.

large portions of the femoral shaft gradually disappeared, apparently through destruction and resorption of the bone; this left gaps in the bone of variable length which were filled by fibrous tissue. In Fig. 4 extensive destruction of the lower end of the femur at 185 days is shown. At 280 days no trace of the lower half of the femur could be seen on the roentgenogram. Pathologic fractures, not associated with tumours, were found as early as the 78th day after irradiation. In Fig. 7 an example is seen at 280 days; the changes here are somewhat similar to those seen in Fig. 3 but are more severe. In this rat the lower half of the right femur, the patella and the tibial epiphysis had all disappeared at 386 days. Bony bars across the femoral shaft, as shown in Fig. 5, were found in more than one third of the animals; these bony bars, on histologic examination, were found to be the remnants of the old spongiosa, devitalized at the time of irradiation (Fig. 6).

Histologic examination of the irradiated bones also showed many instances of a peculiar doubling of the epiphyseal cartilage plates (Fig. 11) and this was demonstrable in roentgenograms (Figs 10 and 12).

The incidence of these lesions, as judged by histological criteria, increased with time after irradiation and it was found in about 25 per cent of the cases. There were various degrees of doubling of the epiphyseal cartilage plates, ranging from incomplete separation to complete division of a plate into two separate plates. The width of the space between the two plates varied and it was generally occupied by cell-producing bone marrow. Occasionally, however, this space was occupied by fibrous tissue containing spicules of bone.

Dense opacities and sclerotic bone lesions. The histologic examination of the irradiated bones showed that in about one third of the cases the newly formed

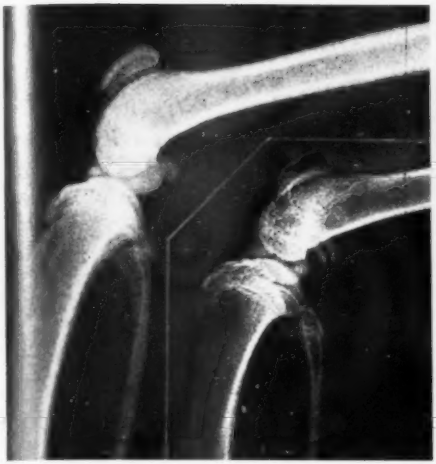
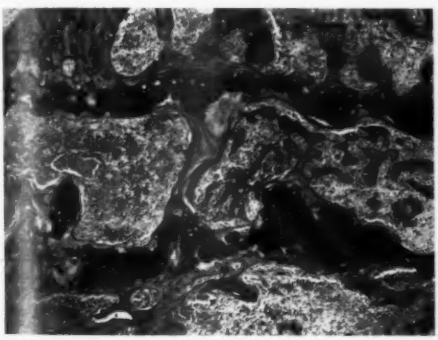


Fig. 8 Fig. 9 Fig. 10

Fig. 8. Roentgenogram of a normal control rat's knee 280 days after beginning of experiment, enlarged 2 1/2 times for comparison with figs. 9, 10, 12 and 19.

Fig. 9. Roentgenogram of right knee of rat enlarged 2 1/2 times (79 days after irradiation). Early patchy osteoporosis in the lower end of femur.

Fig. 10. Roentgenograms of both knees at 280 days after irradiation, enlarged 2 1/2 times. The right femur shows sclerosis and interruption of the epiphyseal line, and osteoporosis in the shaft. The right tibia shows doubling of the epiphyseal plate. The left femur shows interruption of the epiphyseal line and zones of rarefaction in the epiphysis and diaphysis. There is some sclerosis and a doubling of the tibial epiphyseal plate.



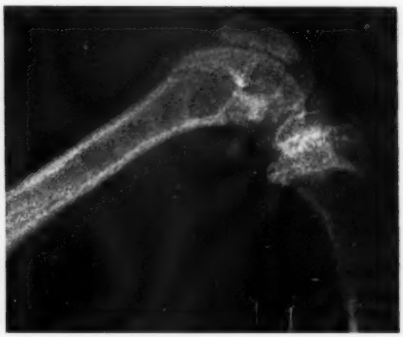


Fig. 11 Fig. 12

Fig. 11. Doubling of the epiphyseal cartilage plate in the tibia of a rat 499 days after irradiation. Hematoxylin and eosin. × 28.

Fig. 12. Roentgenogram 499 days after irradiation. Enlarged 2 1/2 times to show double epiphyseal cartilage plate of left tibia and patches of rarefaction and sclerosis in the femoral epiphysis.

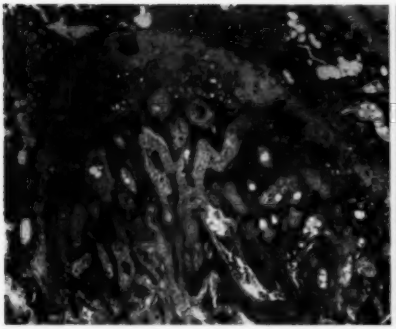


Fig. 13. Thickened epiphyseal cartilage plate and prominent newly formed spongiosa in femur of rat 455 days after irradiation. Hematoxylin and eosin. × 60.

Fig. 14. Roentgenogram 461 days after irradiation. Marked opacity of metaphysis of right femur.

Fig. 15. Roentgenogram 521 days after irradiation. Mottling of right femoral shaft.

spongiosa had not been absorbed properly (see Fig. 13), and this appeared in the roentgen films as an opacity in the metaphysis, as shown in Fig. 14, or as a general mottling of the shaft, as shown in Fig. 15. Similar opacities were frequently seen in the epiphyses of the femur and tibia, at various times after irradiation, and on histologic examination (see Fig. 16) these were found to be due to fibrosis and new bone formation in the damaged marrow spaces in these areas. Some of the opacities were due to the enlarged and thickened cartilage plates with irregular contours. In three instances a dense opacity of this kind was found to be a precursor of an osteogenic sarcoma occurring later at the same site (Figs 17 and 18).

The radiographic appearance of the osteosarcomata. Osteosarcomata were found in 34 animals, and in four instances two independent bone tumours were seen in the same animal. As mentioned above, it was possible in three animals to trace the origin of the tumour to a previously existing focus of osteosclerosis (Figs 17 and 18). In general, however, it was impossible to correlate the site of origin of any of the bone tumours with any particular type of bone lesion that was seen earlier on the roentgen films. Fig. 19 shows the roentgenographic appearance of a bone with an early osteosarcoma in the lower epiphysis of the femur. The changes present in the roentgenogram would scarcely warrant a diagnosis of osteosarcoma, yet the histopathology was quite definite. Thus a tumour may be present before the roentgenogram gives evidence of its presence. Another roentgenogram of an early osteosarcoma is shown in Fig. 20; the changes are more marked and there is an early pathologic fracture. Fig. 21 shows a definite early osteolytic tumour with a pathologic fac-

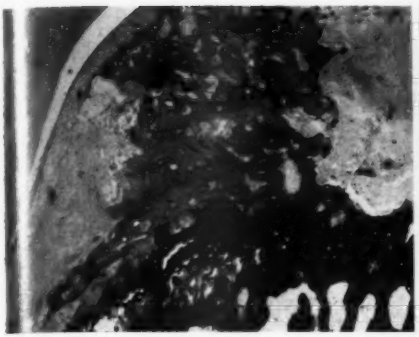


Fig. 16. Thickened cartilage plate and sclerosis of the epiphysis in a rat 566 days after irradiation. Hematoxylin and eosin. × 60

Fig. 17. Roentgenogram 280 days after irradiation. Sclerosis of left tibia.

Fig. 18. Same rat as in fig. 17. 386 days after irradiation. Osteosarcoma of left tibia.

ture of the fibula, and Fig. 22 a more advanced osteolytic tumour with extensive bone destruction and a pathologic fracture of the femur. Most of the bone tumours were of the sclerosing type (Figs 18 and 23). Fig. 24 is an example of a large tumour with more diffuse scattered zones of ossification. Osteolytic types of tumours were not uncommon (Figs 21 and 22).

Fibrosarcomata. A total of 54 soft tissue sarcomata were found in 50 animals and these were easily detectable on the roentgen films; in some instances these tumours were associated with pathologic fractures (Fig. 25), as were some of the osteosarcomata.

The development of bone lesions in time. The changing pattern in the incidence of bone abnormalities is graphically demonstrated in the Diagram below, where the incidence of radiographic changes as a percentage of bones at risk is shown at various intervals after irradiation. It will be noticed that the incidence of bone changes, such as osteolytic foci, areas of sclerosis and pathologic fractures, was higher in the first months of the experiment and decreased with time. Conversely, the incidence of bony bars and osteosarcomata follows a bimodal distribution in time, with two peaks of incidence at about the 400th and 650th days. In some animals, therefore, there was complete healing of the severe damage which was observed at 185 days, and in others the extent of damage was markedly reduced and the lesions became more circumscribed. An example is shown in Fig. 2, where mottling and osteolytic foci, present in the left femur at 185 days, were eventually reduced to a single punched-out lesion at 386 days. The other bones in this animal showed a return to almost normal architecture, with the exception, of course, of the shortening.

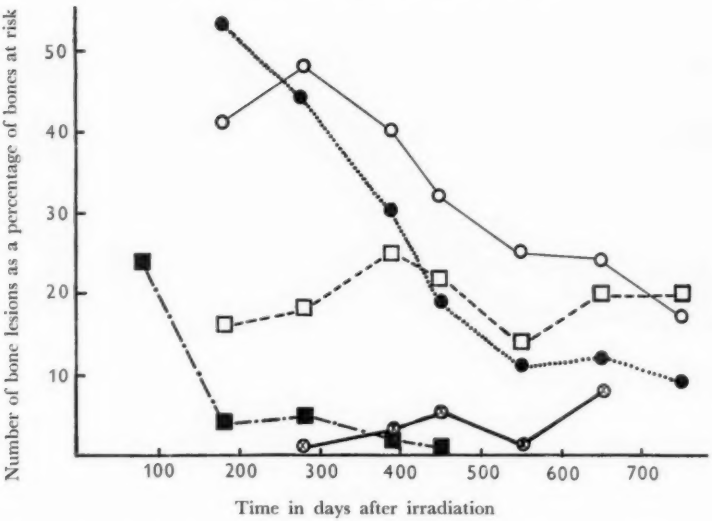


Diagram showing incidence of roentgenographic changes in rats irradiated with 3 000 r gamma rays ● Foci of osteolysis —○ Sclerosis of head or shaft ····· □ Bony bars ·—·—■ Pathologic fractures —⊗ Osteosarcomata

Effects of hormone treatment. As mentioned above, there were no striking differences in the radiographic or histologic appearance of the irradiated bones in rats subjected to different hormone treatment. Hormone treatment, however, had some influence on the incidence of the various lesions: besides the increased incidence and the shortened induction period of osteosarcomata, both hormones, together or separately, increased the incidence of pathologic fractures, bony bars and split epiphyseal cartilage plates.

Discussion

Damage to the epiphysis. An important feature of the experiment now described was the extensive damage to the epiphyseal cartilages caused by 3 000 r external radiation from a Ir^{192} teletherapy source. This damage could be seen both in the roentgenograms and the histologic sections. The cartilage was always greatly thickened, the columns of cartilage cells were irregular and the cells showed great variations of size and staining. Doubling of the epiphyseal cartilage was a frequent feature. Sissons (1955) irradiated the right tibial epiphysis of rats (at 30 days of age) with 190 kV roentgen and measured the growth rate of the tibia over the next hundred days. With increasing dose

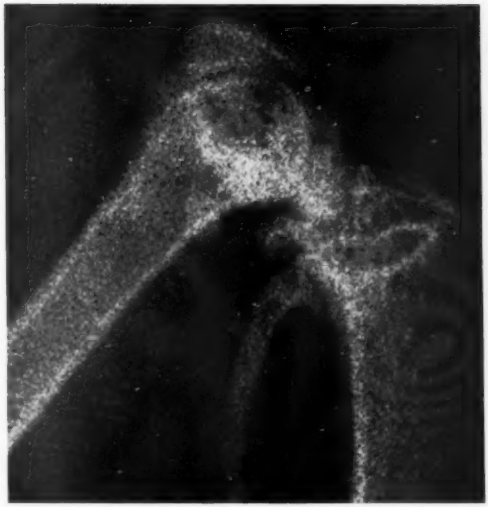


Fig. 19. Roentgenogram of rat 386 days after irradiation. Early osteosarcoma of left lower femoral epiphysis (confirmed by histology). × 2 1/2.

from 400 r to 1 600 r there was progressive interference with growth, and with 1 600 r growth was virtually brought to a standstill. The irradiated epiphyseal plates, despite the reduction in their growth rate, were as thick as or thicker than the controls. With 1 200 r extreme disorganisation of the cartilage columns was noted. This dose of 190 kV roentgen would administer a dose to the bone comparable with the 3 000 r gamma rays from Ir^{192} used in our experiments. Damage to the proliferating cartilage cells would appear to be an important cause of some of the abnormalities which appear subsequently in the bone. The stunting of growth can be attributed to this cause, and some of the osteosarcomata appeared to arise near the epiphyseal cartilage.

A summary of the observations of other investigators. LOONEY and coll. (1955) described under three headings the bone changes visible in roentgenograms of patients who had received radium salts therapeutically: (1) minimal lesions consisting of punched-out areas of decreased density which, when multiple, caused a streaked appearance of the bone, (2) areas of apparently increased density usually associated closely with areas of decreased density which often gave the bone a 'moth-eaten' appearance, and (3) areas of aseptic necrosis with sequestration. In later stages, as also reported by AUB et coll. (1952),

Figs 20—22. Roentgenograms of rat 464, 635, and, respectively 434 days after irradiation.
Fig. 20 (Upper left): Pathologic fracture and early osteosarcoma of lower epiphysis of right femur.
Fig. 21 (Lower left): Osteosarcoma of the right tibia and fracture of the right fibula.
Fig. 22 (Right): Osteolytic sarcoma and pathologic fracture of left femur.

pathologic fractures and malignancy often complicated the picture described above.

Bone changes produced by external irradiation differ from those produced by internal deposition of radioactive materials. There are three reasons for this, namely the differences in the relative biological effectiveness of the various ionizing radiations, the selective distribution of radio-isotopes in bones, which influences the distribution of lesions, and the persistance of radio-isotopes in bone for comparatively long periods of time which probably influences the reparative processes in bone. As mentioned above, GRATZEK and coll. (1945) described the appearances of roentgenologically demonstrable lesions in patients who had received external irradiation for malignant conditions of the genitalia. The most prominent changes in this series consisted of aseptic necrosis of the head and neck of the femur, sclerotic changes and pathologic fractures. In contrast, NEUHAUSER and coll. (1952) showed that irradiation of growing bones, especially in children aged two years or under, caused stunting of growth and severe pathologic changes. As a late compli a-

Fig. 23. Roentgenogram of rat 386 days after irradiation. Sclerosing osteosarcoma of left tibia.

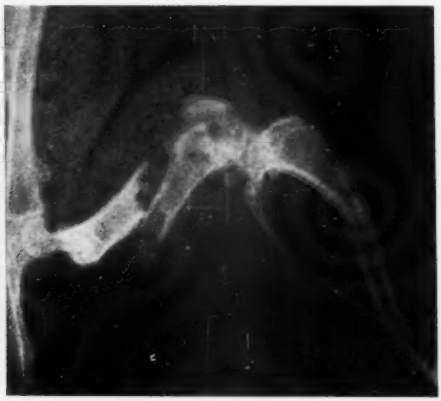


Fig. 24. Roentgenogram 525 days after irradiation. Fibrosarcoma and pathologic fracture involving left femur.

tion of external irradiation of bone CAHAN et coll. (1948) and SABANAS et coll. (1956) described a number of bone sarcomata.

Comparison of our findings with those of other investigators. The changes described in the present experiment were more varied and more frequent than those described in irradiated patients by GRATZEK et coll. (1945), and may be summarized as follows:

1. After external irradiation of bone there is a latent period, during which radiographical lesions are minimal and essentially limited to stunting of growth and changes associated with lesions of the soft tissues.

2. The frequency of bone lesions reaches a maximum about 6 months after irradiation, after which (contrary to what happens with the majority of bone-seeking isotopes) healing takes place in a number of bones.

3. Bone lesions are distributed in the whole field of irradiation, and the epiphyses of bones are often damaged, whereas with most of the bone-seeking radio-isotopes, lesions in the epiphyses are minimal.

4. Osteosarcomata occur in about 29 per cent of the irradiated animals, and, on roentgenograms, are sometimes preceded by a massive sclerosis of bone.

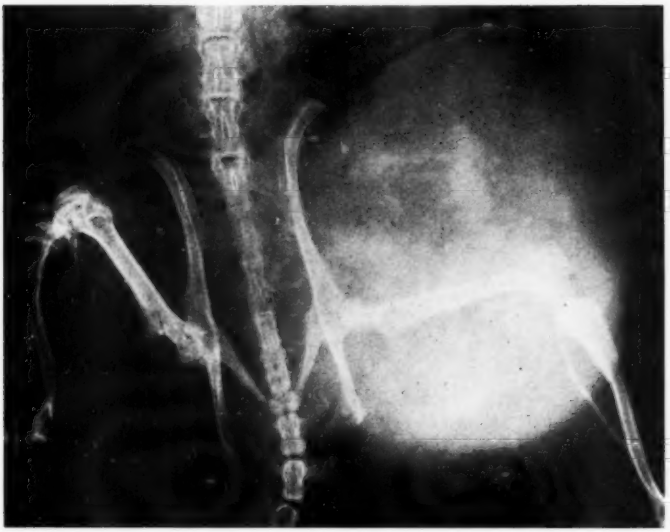


Fig. 25. Roentgenogram of rat 307 days after irradiation. Huge osteosarcoma of left femur.

Acknowledgements

We are indebted to Professor J. S. Mitchell for his constant encouragement and advice. The investigation was begun while one of us (H. L.) was working in the Department of Radiotherapeutics of the University of Cambridge under a special grant from the British Empire Cancer Campaign which is gratefully acknowledged. One of us (D. B. C.) held a British Empire Cancer Campaign Research Fellowship during the period of the investigation.

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Our grateful thanks go to Miss N. C. Burr of the Department of Pathology, University of Cambridge, for her splendid care of the animals and technical assistance.

SUMMARY

The development of bone lesions was followed radiographically after a single dose of 3000 r γ-rays from a Ir^{192} source applied to both knees of 136 rats. Stunted growth of bone was the earliest detectable change. At 6 months, zones of osteolysis and osteosclerosis were frequent. Transverse bars of bone, pathologic fractures and destruction of bone were also seen; some lesions persisted, others healed. Epiphyseal cartilages were thickened in 100 % and doubled in 25 % of irradiated rats. Osteosarcomata developed in 34 out of 116 rats surviving more than 250 days.

ZUSAMMENFASSUNG

Die Entstehung von Knochenschäden wurde nach Verabreichung einer Einzeldosis von Ir = 3 000 r γ-Strahlen auf beide Knie von 136 Ratten röntgenologisch verfolgt. Verminderung des Knochenwachstums war das erste erkennbare Symptom. Nach 6 Monaten fand man häufig Osteolyse und Osteosklerose. Auch sah man transversale Knochenbälkchen, pathologische Frakturen und Knochendestruktion. Einige dieser Schäden waren bestehend, andere heilten ab. Eine Verdickung des Epiphysenknorpels fand man in 100 %, eine Verdoppelung in 25 % der bestrahlten Ratten. Von 116 Ratten, die mehr als 250 Tage überlebten, entwickelten sich in 34 Fällen Osteosarkome.

RÉSUMÉ

Les auteurs ont suivi radiographiquement le développement de lésions osseuses consécutives à une dose unique de 3 000 r de rayons gamma émis par une source de Ir^{192}, administrée sur les deux genoux de 136 rats. La première modification décelable a été un défaut de croissance de l'os. A six mois, les zones d'ostéolyse et d'ostéosclérose étaient fréquentes. On observait aussi des stries osseuses transversales, des fractures pathologiques, et des destructions osseuses. Certaines lésions persistèrent, d'autres guérirent. Les cartilages épiphysaires étaient épaissis chez 100 % et doublés chez 25 % des rats irradiés. Des ostéosarcomes sont apparus chez 34 des 116 rats qui ont survécu plus que de 250 jours.

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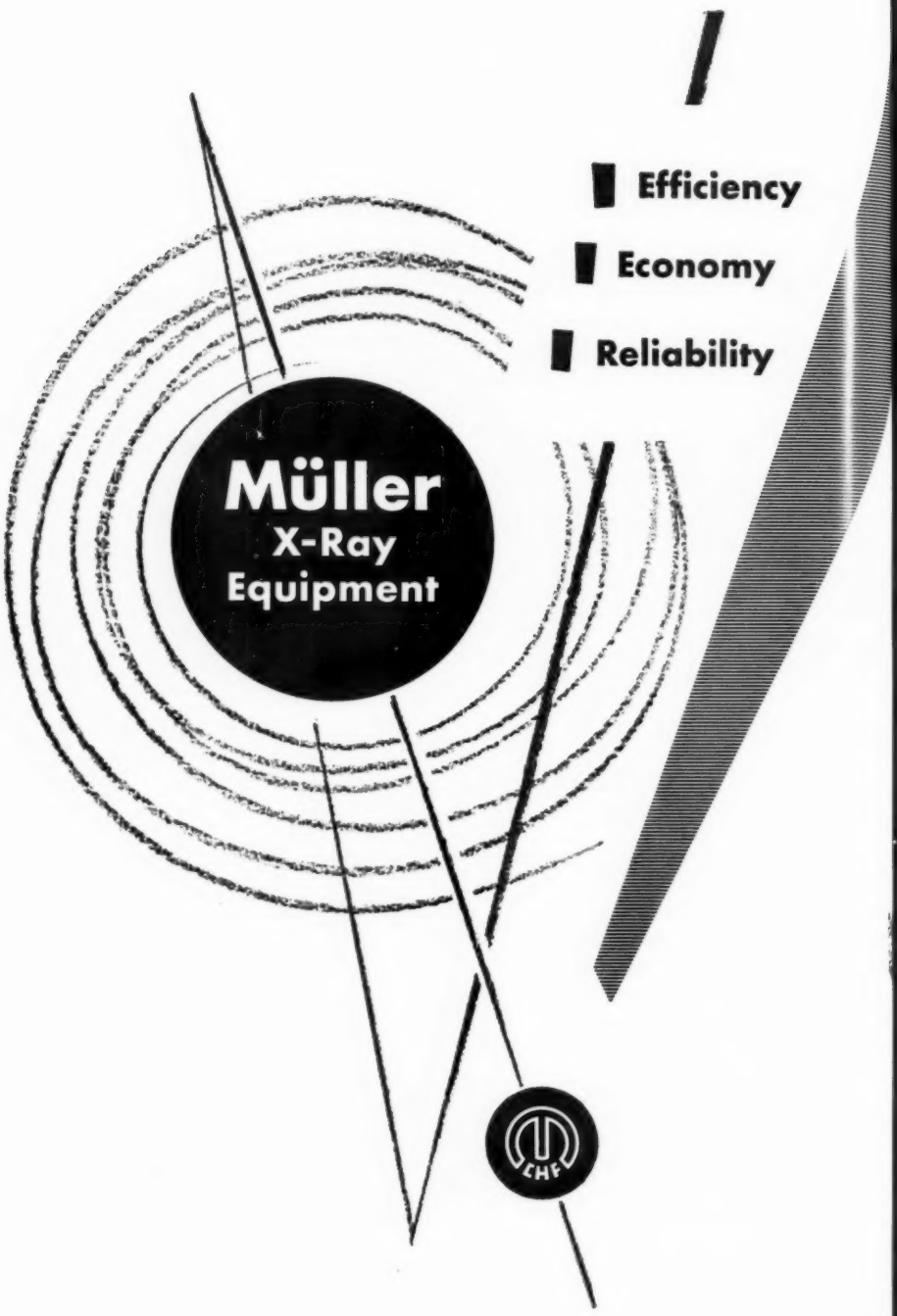
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FROM THE RESEARCH UNIT IN RADIOBIOLOGY, BRITISH EMPIRE CANCER CAMPAIGN,
MOUNT VERNON HOSPITAL, NORTHWOOD, MIDDLESEX, ENGLAND

STATISTICAL ASPECTS OF PLANNING CLINICAL EXPERIMENTS IN CANCER THERAPY

by

J. W. BOAG

An important criterion for assessing the value of any new technique of cancer therapy is the proportion of long-term symptom-free survivors achieved by its use. This is not the only possible criterion, and in those sites where permanent cures are still exceedingly rare it may be more appropriate to find some way of measuring the palliative value of the treatment. There are, however, undoubtedly many sites in which the proportion of long-term survivors is a good criterion of success. It is therefore important to find ways of planning and evaluating a clinical test of any new treatment method which shall determine this proportion of long-term survivors as accurately and rapidly as possible.

Since it is impossible to say in any individual case whether an initially good response will be maintained, it is necessary to study the mortality experience of large groups of patients treated a long time ago in order to discover and utilise any regularities presented by such data. Some ten years ago it was shown (1, 2) that the survival expectation of the unsuccessfully treated cases among cancer patients treated by radiotherapy or by surgery followed by radiotherapy (i. e. those who subsequently died with a persistence or recurrence of the disease) did, in fact, show a striking regularity. Although

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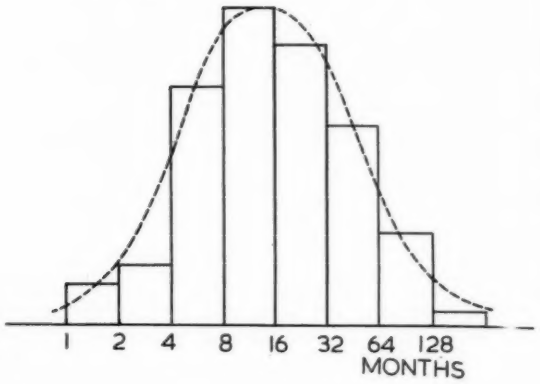

Fig. 1. Distribution of survival times for 939 patients with carcinoma of the cervix who died with cancer present.

individual survival times of such patients varied from less than one month up to many years, the frequency histogram for any large group was of a characteristic form, and much the same in one treatment centre as in another for comparable cases. It was an unsymmetrical or 'skew' curve which became relatively symmetrical, however, when the histogram was drawn on a logarithmic time scale, and in this form it could be fitted very closely by the 'normal' or 'Gaussian' curve.

An illustration of this data collected 10 years ago is provided by Fig. 1. This refers to 939 cases of carcinoma of the cervix (1) of all clinical stages, treated at one centre during the years 1929 to 1939, all of whom subsequently died with cancer present. In this diagram the time scale of the histogram is logarithmic, that is to say, equal intervals along the axis of abscissae represent the same multiplying factor. It can be seen that the normal curve which is superimposed on the histogram provides an excellent fit.

A better test of this hypothesis is to plot the data on logarithmic probability graph paper. Any normal distribution plotted in this way appears as a straight line. In Fig. 2 the Copenhagen data recently published by SØRENSEN have been plotted in this way. These data refer to 581 patients with carcinoma of the cervix who died with cancer present. Fig. 3 shows the survival time distribution for some 2 200 carcinoma of the cervix patients who died with disease present, including both the foregoing groups and two others as well, plotted on log-probability paper. The straight line based on all the points confirms that this mixed sample of data is excellently fitted by a lognormal curve. The separate samples from different epochs and different treatment centres all cluster closely around the mean line, and the differences between them are hardly significant and certainly not large. All the samples contained a mixture

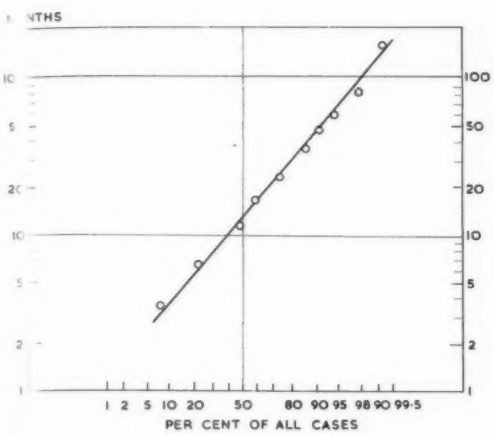

Fig. 2

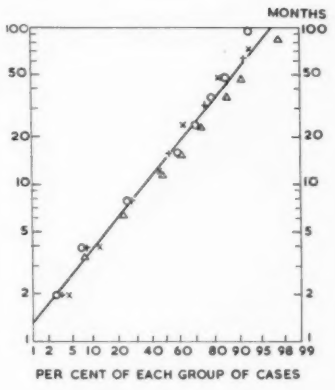

Fig. 3

Fig. 2. Distribution of survival times, plotted on logarithmic probability paper, for 581 cases of carcinoma of the cervix patients who died with cancer present. After SØRENSEN (3).

Fig. 3. Plot on logarithmic probability paper of the survival time distribution for four groups of patients with carcinoma of the cervix, all of whom died with cancer present. The different groups of patients are referred to as follows:

× 497 patients treated in centre E
+ 939 » » » » M
○ 269 » » » » N
△ 581 » » » » D

of all clinical stages. When one separates the data into stage groups, different lines are obtained which remain approximately parallel: the mean log survival time varies according to clinical stage but the standard deviation does not change much.

To choose another site, we may examine the survival experience of unsuccessfully treated cases of carcinoma of the breast. Some 4 000 such cases drawn from four different treatment centres are presented in Fig. 4. The straight line is the best line for all the points and the separate groups of data are designated by different types of point. (In preparing these curves, cases having survival < 1 month have been excluded as different centres appeared to have different policies for dealing with such advanced and probably often moribund cases. The numbers of such cases are small, usually only 2 or 3 % of the whole group.) Extensive data of this same type have previously been published for carcinoma of the mouth and throat. In all cases the distributions obtained are adequately fitted, and often exceedingly well fitted, by lognormal curves. It would be of considerable interest to obtain similar data for other

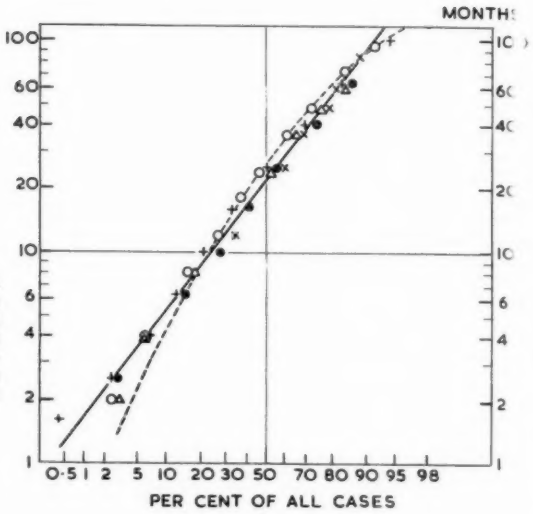

Fig. 4. Logarithmic probability plot of the distribution of survival time for some 4 000 unsuccessfully treated patients with carcinoma of the breast who subsequently died with the disease present. The different groups of patients are referred to as follows:

○ 2 228 cases treated in centre E
\+ 709 » » » » V
× 436 » » » » CH
△ 555 » » » » RM
● 241 » » » » RM

sites, and there must be many centres from whose past records such data could be extracted without great trouble.

Information about the shape of the survival curve for unsuccessful cases can be utilised to assist in assessing the long-term cure rate, as has been shown elsewhere (1, 2). Naturally, any statistical model of a clinical treatment series which is set up must not be interpreted too rigidly and it would be unwise to use as sole criterion of success the value of 'C' i. e. the parameter which represents the proportion cured. It is better to look upon a statistical model as a framework which permits a limited extrapolation of the results to be made, say to 5, 10, or 15 years ahead.

A model of this kind can also be used in planning a clinical trial of a new type of treatment and in developing statistical methods appropriate to such an experiment. The statistical model for a treatment series which is suggested by the data presented in Figs 1 to 4 is illustrated in Fig. 5. Patients entering the treatment series are represented by the square of unit area. Those who are successfully treated are represented by the square of area 'C'. The proportion (I—C), will have a mortality experience which is represented by the upper curve, the form of this curve being lognormal and depending on two constants μ, the mean, and σ, the standard deviation of the logtimes.

We may use the above information on the distribution of survival time to examine the kind of data which is likely to be available for statistical analysis after the use of an experimental treatment technique for any specified length

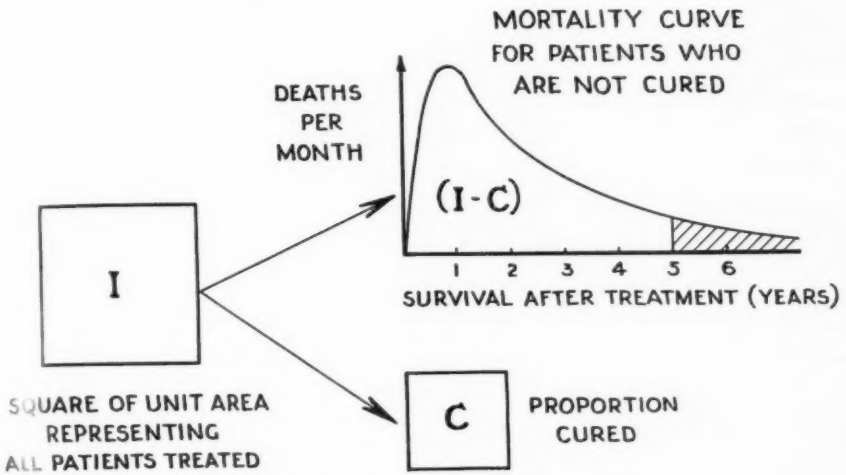

Fig. 5. Statistical model of a clinical treatment series.

of time. To do this, we have to make an assumption about the proportion of long-term survivors which would be found by the use of this treatment in a very large sample, and we must also choose constants for the lognormal distribution which will be appropriate to the site and stage of the disease to be treated. Having chosen all these constants and also the rate of intake of patients to the treatment series, we can then produce by random procedures a typical sample of results.

To illustrate this, Fig. 6 represents an intake of 10 patients per month into a treatment series where the long-term survivors would be 30 % in a very large sample, and for which the lognormal curve is that appropriate to carcinoma of the mouth and throat.

The top line in Fig. 6 is marked out in monthly intervals and the ten dots in each interval represent 10 patients. One could allow these figures for monthly intake to fluctuate randomly about 10, as they would in an actual experiment, but it is hardly worth while to do so. From tables of random numbers we can determine how many in each monthly group of 10 are to be considered as long-term survivors. This number will vary from 0 to 10 in individual groups but will average 3 over any large number of monthly groups. The remainder of the 10 must have survival times which are a random sample from the assumed lognormal distribution.

Such a random selection can be made in various ways, mechanical or statistical, which need not be considered in detail here. Typical samples are

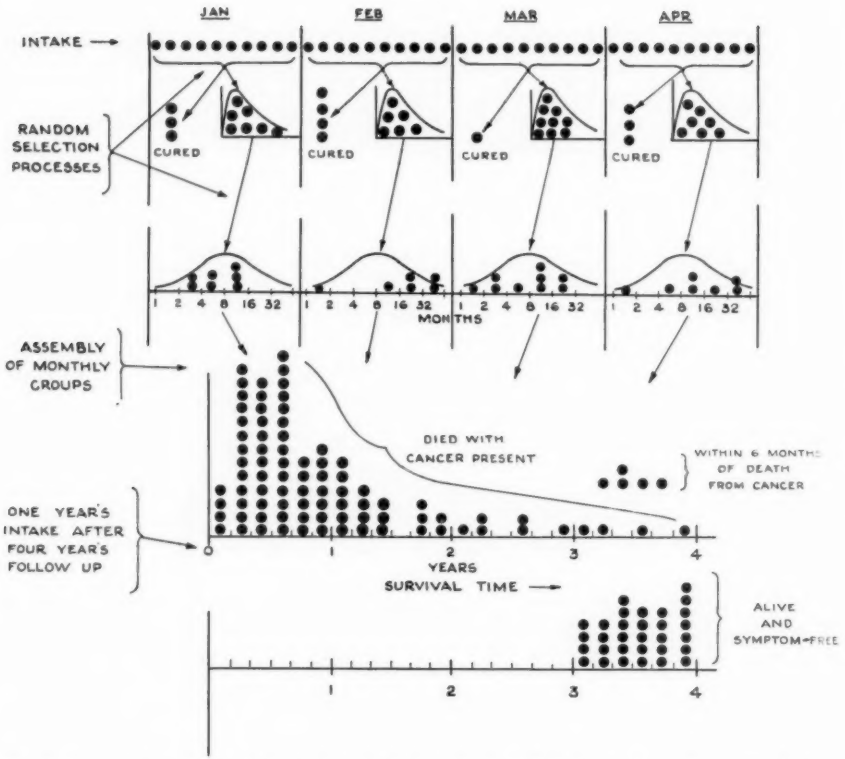

Fig. 6. Construction of a typical set of results in hypothetical clinical experiment in cancer therapy.

however illustrated in Fig. 6, and the arrows show how these may be put together at any desired time after commencing the treatment series to give a complete picture of a typical set of results up to that date.

It may not be clear what is the value of this whole 'Monte Carlo' experiment for we cannot expect to get out of it any information about the actual value of 'C' for the clinical experiment which is contemplated. We can, however, see what a typical set of results will look like for 'C' = 20, 30, 40, or 50 %, and if we make repeated random trials of this kind we can use the typical samples of data they provide to test various possible techniques of statistical analysis with a view to finding the most sensitive and convenient method of drawing information on long-term survival rate from the actual clinical data, as this accumulates. This is by no means an unnecessary task. The statistical

cr ria which have generally been used hitherto in cancer therapy are of the si plest kind, but nevertheless the validity of any tests of significance used h to be examined very carefully, in view of the relatively small numbers of ca s on which such tests may have to be made. For instance 'mean survival ti ' has sometimes been used as a criterion of success and in view of the lo ormal distribution of survival time, the mean is not a suitable represent- at e for comparing different groups.

he 'Monte Carlo' tests outlined above can provide direct numerical an vers to some of these problems of 'small samples' which are too difficult fo exact mathematical analysis. They can also demonstrate to a clinician th kind of data which an experiment may be expected to yield on given as mptions, optimistic or pessimistic, about long-term survival rate.

SUMMARY

A statistical model of a clinical treatment series is set up on the assumption that survival times of patients not cured are log-normally distributed. It is shown how this statistical model may be used to provide random samples of the kind of data likely to be obtained from an actual clinical experiment. Such data can be used to test different methods of statistical analysis and thus discover the best one to use in an actual clinical treatment series.

ZUSAMMENFASSUNG

Ein statistisches Modell einer klinischen Behandlungsserie wird unter der Annahme aufgestellt, dass die Überlebenszeiten der nicht geheilten Patienten normal-logarithmisch verteilt sind. Es wird gezeigt, dass dieses statistische Modell benutzt werden kann, um zufallsbedingte Beispiele solcher Daten zu bestimmen, wie sie ähnlich aus aktuellen klinischen Experimenten erzielt werden können. Derartige Daten können dazu benutzt werden, verschiedene Methoden der statistischen Analyse zu testen und auf diese Weise die Methode entdecken, welche in einer aktuellen klinischen Behandlungsserie am besten ist.

RÉSUMÉ

L'auteur a établi un modèle statistique d'une série de traitement clinique en supposant que la distribution des logarithmes des temps de survie des malades non guéris a une distribution normale. Il montre que ce modèle statistique peut servir à fournir des échantillons soumis au hasard, conformes aux données qu'on peut obtenir d'une véritable expérimentation clinique. Ces données peuvent être utilisées pour tester différentes méthodes d'analyse statistique et pour découvrir celle qui convient le mieux pour une véritable série de traitement clinique.

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FROM THE MEDICAL AND PHYSICAL SECTION OF THE STATE INSTITUTE OF RADIATION HYGIENE (DIRECTOR: KRISTIAN KOREN), RIKSHOSPITALET, OSLO, NORWAY

DETERMINATION OF THE OVARY DOSE IN DIAGNOSTIC ROENTGEN PROCEDURES

by

FINN DEVIK, JON FLATBY and LEIV BERTEIG

The genetically significant dose of radiation from medical roentgenography to a population may be calculated if sufficient factors and data are known: the average radiation dose to the gonads from each type of examination, the total number of examinations per annum, the distributions of the various types of examination in terms of age and sex, the number of individuals in the population, and the child expectancy as a function of age and sex (OSBORN and SMITH 1956, ICRP and ICRU 1957, United Nations Scientific Committee on the Effects of Atomic Radiation 1958).

Whereas the dose to the testicles in the male may easily be measured directly, such measurement of dose to the ovaries in females is not possible. An estimation of the dose to the ovaries from diagnostic roentgen exposures may be made in various ways:

1. By direct measurements in postmortem material (MACGREGOR and OLIVER 1952, STANFORD and VANCE 1955, FELDMAN et coll. 1958, HARTUNG 1958).

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Fig. 1. Position of the 35 mm ionization chamber. The axis of the chamber, placed according to the text, shown by arrow.

Fig. 2. The phantom showing the openings of the two tubes leading to the sites of the ovaries.

Fig. 2

2. By constructing a phantom, representative of an average woman of mean fertile age, and taking direct measurements at the site of the ovaries (KOREN and MAUDAL 1957, BILLINGS et coll. 1957, LAUGHLIN et coll. 1957, CLAYTON et coll. 1957, LINCOLN and GUPTON 1958, NORWOOD et coll. 1959, KLOTZ and SEELENTAG 1958, MOHR et coll. 1959, et alios).

3. Measurements in live subjects by readings from ionization chambers placed in the rectum or vagina or on the skin and deducing the dose to the ovaries from such data (HAMMER-JACOBSEN 1957, LARSSON 1958, SEELENTAG et coll. 1958, MOHR 1958, LÖSSL 1957, ADRAN and CROOKS 1957, SPIERS 1957, OSBORN 1959, et alios).

A combination of these methods has been chosen by several of the authors quoted above.

It was found necessary to examine and evaluate these methods for determining the dose to the ovaries in an investigation of the gonad radiation load from the medical use of roentgen radiation in the potentially reproductive section of the population in Norway.

Instrumentation. Dose measurements were made with a Kondiometer from Physikalisch-Technische Werkstätten, Freiburg. The ionization chambers were calibrated and the wavelength and directional dependence determined; the results in the diagnostic range agreed well with other results published (SEELENTAG 1957). These effects were considered unlikely to introduce any error of importance in our cadaver or phantom measurements. Cylindric ionization chambers 15 mm in diameter and 35 mm in length were most frequently used. With a measuring range from a few milliroentgen to about 700 mr they cover most of the doses, and the dimensions allow the chambers to be employed satisfactorily for body cavity measurements.

Measurements at autopsy. Six female bodies were subjected to various diagnostic procedures in the supine position on a Bucky table. Ionization chambers protected by a double layer of thin rubber condoms were placed in contact with one or both ovaries, in the rectum, in the vagina and on the skin of the abdomen and the back; roentgenograms recorded the position of the chambers. The investigations were performed with a single-wave Siemens roentgen unit, the tube being fitted with a multiple leaf diaphragm and an illuminated field-size indicator. The total filtration was about 1.5 mm Al. The direct palpation possible in these cases was of importance for a better understanding and evaluation of the variables obtaining in both direct and indirect determinations of the ovary dose. Wide variations in the ratios of the doses recorded were found in spite of reasonably reproducible results in each cadaver. From the five different diagnostic procedures undertaken, the results of an 'abdomen, general view' exposure are presented in the Table below:

65 kV, HVL = 1.4 mm Al, FFD = 100 cm, film size 30 × 40 cm²

Body No.	Ovary/skin %	Dose ratios		Transmission %
		Ovary/vagina	Ovary/rectum	
I	12.9	2.1	2.9	1.3
II	7.0	1.8		0.56
	6.8	1.5		
III	13.1	2.2	3.1	1.4
IV	13.8	1.0	1.4	2.0
	17.0	1.4	1.9	2.4
V	3.6	0.51	0.77	
	3.8	0.55	0.76	0.56
	4.1	0.47	0.70	
	4.0			
	3.6			
VI	27	2.8		
	24			
	27			2.3
	26	2.4	2.2	
	23	2.2	2.2	
Phantom	9.1		1.3	appr. 1.0

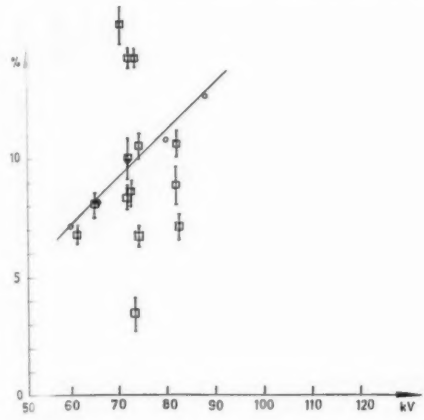

Fig. 3. Transmission ratio rectum/skin in pelvis a.p. exposures, observed in the phantom (○) and in 14 patients (□).

The variations are regarded as due to individual differences in the anatomical relations, although bodies were chosen that did not differ much from that of a young adult woman of 'average' size. It also became clear that the dose ratios, e. g. ovary/rectum, show considerable variations with the type of investigation. From these pilot investigations it was concluded that representative values of the ovary dose cannot be obtained unless a great number of bodies are investigated by a variety of diagnostic procedures with different roentgen apparatus. For practical reasons such a programme cannot be carried out and differences between living and dead bodies, e. g. with respect to muscle tonus, active movements, flexibility, will almost certainly affect the true values.

The results further stressed the necessity of defining the usual position of the ovaries, as well as the situation of the ionization chambers as related to the anatomic structures for indirect dose determinations. Although considerable variations in the location of the ovaries, depending on various anatomical, physiologic and pathologic factors are known to exist, textbooks of anatomy describe the usual sites as being in the ovarian fossae of the pelvic wall. For the present purpose this is taken as the point of departure for arriving at a representative average position for the ovary, as follows: the centre is taken as lying at a point 8 mm medial to the peritoneum of the lateral pelvic wall, 8 mm below and behind a horizontal line joining the two great sciatic notches at a point closest to the ileopectineal line. A line through the centre of each ovary crossing this horizontal line would lie perpendicular to a plane between the two ileopectineal lines. Fig. 1 illustrates the location of the axis of the ionization chamber during measurements performed at autopsy.

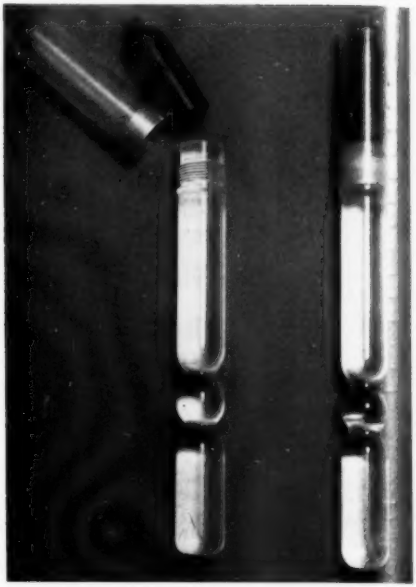

Fig. 4. Polystyrene rod used for the insertion of a 15 mm × 35 mm ionization chamber into the rectum.

Use of a phantom to assess the gonad dose. An ideal phantom, incorporating a true average of all the factors and properties which are of importance in determining the ovary dose, is in practice hardly feasible. An approximation of the ideal with respect to some of the factors, e. g. dimensions and tissue-like properties in the absorption of radiation, may, however, be fairly easily established. Such a phantom was constructed around a skeleton to include the femora, pelvis, spine and ribs. In our first attempts we tried 'Mix D' (JONES and RAINE 1949) for modelling the soft tissues. The tendency of 'Mix D' to form cracks when cooling and hardening caused considerable trouble. Another 'tissue' mixture 'M 3' (MARKUS 1956) was found to be better in this respect, and was used for the pelvic section of the phantom; 'Mix D' was retained for the remaining parts. Roentgenographic control and symmetry directional measurements with ionization chambers during the exposures showed that a satisfactory homogeneity was being obtained. Plastic bags filled with sawdust were used to simulate the lungs. Two thin-walled plastic tubes for holding the ionization chambers were moulded in the correct positions, the lumen of each tube above the chamber being closed by a polystyrene rod, which also served as a support for the chamber (Fig. 2).

The phantom was, for practical reasons, divided into two parts horizontally above the iliac crests. Since statistical data on the required dimensions were

Fig. 5. Roentgenogram showing the ionization chamber inserted into the rectum by means of the polystyrene rod.

not available, these had to be estimated. The dimensions of the phantom were as follows: knee-neck 90 cm, corresponding to a height of about 162 cm, bust measurement 96 cm, waist measurement 70 cm, hip measurement 86 cm. In 1952 the average Norwegian woman in the 20—29 age group was 164 cm in height and weighed 60.2 kg. (For this 'size', suppliers of clothing usually regard the following as standard measurements: bust 94 cm, waist 69 cm, and hip 102 cm.)

In order to check the radiation transmission in a region close to the ovaries, where comparative measurements in living patients can also be carried out, the phantom was provided with a 'rectum'. This was constructed so as to locate the chamber in a position determined from a series of roentgenograms of the sacral region in living subjects (Fig. 5). From dose measurements obtained in the rectum of patients undergoing diagnostic roentgen examination (pelvis a.p.) and from measurements on the phantom with the same apparatus and technique, rectum/skin transmission ratios were determined. The results may be seen in Fig. 3. The points from 14 patients chosen at random are scattered fairly evenly around the line obtained from the phantom. This indicates a reasonable choice for the dimensions of the phantom.

Apart from serving the main object, namely that of obtaining dose measurements at the site of the ovaries, the phantom also offers the possibility of serving as a reference standard for comparing different techniques and equipment. The phantom has been found a handy and useful instrument for experiments aiming at the reduction of the ovary dose. The main shortcomings of he

phantom are that it is rigid, insensitive to position effects, and is not capable of indicating the effects of roentgenography when positive and negative contrast techniques are employed.

Indirect measurements on patients. Since the insertion of an ionization chamber into the rectum is generally less objectionable than when it is introduced into the vagina, and since we found that a chamber in the rectum could be placed closer to the ovaries than one in the vagina, the former method was preferred in most cases.

In order that the ionization chamber could be placed in a defined and reproducible position, the chamber was mounted on a polystyrene rod, 15 mm in diameter (Fig. 4). The chamber was inserted into the rectum so that it lay 10 cm from the anal orifice. Any movement of the rod was prevented by adhesive tape and a circular groove on the rod for the anal sphincter. This arrangement placed the chamber near the anterior wall of the rectum and close to the transverse projection of the site of the ovaries, as shown roentgenographically in Fig. 5. With a distance from the anterior wall of the abdomen about the same as that to the ovaries, it is considered that the rectum in this way receives a dose in fairly good approximation to the ovary dose in all a.p. exposures. It may be added, that an ovary/rectum dose ratio of about 1.1 to 1.3 was noted for various a.p. exposures.

Dose ratios may in general be measured in the phantom for all types of exposures, but each value can only be applied for the same conditions (instrumentation, technique, etc). When the ovaries are irradiated asymmetrically, estimation of the dose ratios are of some interest. For a lateral view of the sacrum, for instance, we found a ratio mean ovary dose/rectal dose between 1.5 and 3.0; for an examination of one hip we have measured dose ratios from 0.8 to 3.5. The upper limit was also reached in our cadaver measurements. Exposures of this type are relatively infrequent and dose ratios of about 1 (0.8 to 1.5) are the general rule.

Conclusions

The practical determination of the gonad dose in women undergoing roentgen diagnostic procedures must be performed by indirect measurements. It may be concluded from our investigations that acceptable values for the ovary dose may be obtained by a special technique of in situ measurements on the rectum supplemented by phantom measurements. It is assumed that for certain examinations the number of clinical measurements undertaken may be reduced in favour of phantom measurements. The phantom moreover enables the correcting factor of the measured rectal dose and the true ovary dose to be estimated. In most cases, however, this factor does not appear, with the technique employed, to vary very much. The importance of the employment of the phantom as a reference standard must be emphasized.

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SUMMARY

The estimation of the ovary dose from diagnostic roentgen exposures by direct measurements in postmortem material and in a phantom and in indirect measurements in living subjects is discussed. The construction of the phantom that has been developed is described.

ZUSAMMENFASSUNG

Mit Hilfe direkter Messungen an Leichenmaterial und einem Phantom, und indirekten Messungen an Lebenden wird die Bestimmung der Ovariumstrahlendosis im Zusammenhang mit diagnostischen Röntgenexponierungen besprochen. Der Aufbau des Phantoms, das entwickelt worden war, wird beschrieben.

RÉSUMÉ

Les auteurs étudient, par des mesures directes sur le cadavre et sur un fantôme et par des mesures indirectes sur le sujet vivant, la dose reçue par les ovaires au cours d'examens radiographiques. Ils décrivent la construction du fantôme qu'ils ont mis au point.

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ATTEMPTS TO INFLUENCE THE ELIMINATION OF RADIOSTRONTIUM

by

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Many attempts have been made to influence the elimination of Sr^{90} and to minimize its retention in the skeleton. Of the different approaches made, those involving complexing or chelating agents have been the most prominent.

SCHUBERT and WALLACE (1950) studied the distribution and excretion of radiostrontium in rats treated with zirconium or sodium citrate. Early administration of these agents resulted in an increase in the excretion of radiostrontium which, however, was not significant. In the late-treated group the metabolism was not influenced.

COHN and GONG (1953) gave zirconium citrate before the administration of radiostrontium to rats. The skeletal content decreased 40 % in comparison with the controls. Na-EDTA and Ca-EDTA and a combination of zirconium citrate and BAL were without effect. According to VAUGHAN and TUTT (1953), $CaNa_2$-EDTA had no influence on the excretion of radiostrontium in rabbits.

An infusion of Na-EDTA changed the excretion pattern of Sr^{85} in man (SPENCER et coll. 1958). An initial depression of the urinary excretion was followed by increased excretion. The cumulative excretion was not in excess of that of the controls.

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CATSCH and MELCHINGER (1959) investigated the effect of a number of agents. After early administration, the best effect was obtained with zirconium citrate which reduced the skeletal deposition by about 40 %. Poly- and metaphosphates gave approximetely 30 % and some chelating agents not better than about 15 %. Delayed treatment had no effect.

ITO and TSURUFUJI (1959) examined the effect of citrates, tricarballylates, citraconates, tartrates, and lactates injected immediately after the administration of Sr^{90} to rats. In all the treated groups, a decrease of radiostrontium deposition in the skull was observed. The best effect was obtained with tricarballylate which reduced the deposition 25 %.

The influence of sodium calcium citrate was also investigated by ITO and TSURUFUJI. About 50 % of the citrate was excreted in 6 hours after the administration of Sr^{90}. A very large quantity of citrate was excreted in the urine carrying radiostrontium; the larger the amount of citrate given, the greater was the urinary excretion of both the citrate and radiostrontium.

Since the attempts to hasten the excretion of the incorporated radiostrontium by means of chelating agents have given only little success, another approach to the problem must be tried. One possibility is offered by the carrier effect in which the excretion and distribution of carrier-free radionuclide can be affected by dilution with a stable isotope of Sr. Because of the close chemical relation between Ca and Sr, some kind of nonisotopic carrier effect can be expected by dilution with Ca.

As early as 1947 HAMILTON et coll. suggested the use of inactive strontium. In the study of KIDMAN et coll. (1950), however, a strontium carrier, in the quantity they gave, was without effect on the retention or excretion of active strontium in rabbits, whereas the retention was greater in animals on a low calcium intake than in those on a high calcium intake, and in young as compared to older animals. Their carrier dose was very low, however, only 0.01 to 0.02 g Sr/kg bodyweight.

MACDONALD (1955) found it desirable to examine the effects of massive doses of stable strontium and calcium salts on Sr^{90} retention. Large quantities of $CaCl_2$, given before or simultaneously with Sr^{90}, increased the retention of Sr^{90} significantly but inactive strontium administered 1/2 min before or after decreased the retention. Treatment 1/2 hour after the injection of Sr^{90} had no effect. MACDONALD regarded the results as an apparent anomaly.

Diverging results were obtained by SPENCER et coll. (1956 and 1958). In their first study, calcium gluconate, administered simultaneously with Sr^{85} to human beings, significantly increased the excretion of strontium. In a second study the calcium and radiostrontium excretion in urine increased markedly when calcium gluconate was administered intravenously or NH_4Cl was given orally. The effects of the two agents were additive. A high calcium diet was also effective in promoting urinary excretion of radiostrontium.

GROSS et coll. (1954) in their study could not find any influence of ingested

s ble strontium on the metabolism of radiostrontium. According to HARRISON e coll., carrier strontium has relatively little effect in the retention of an oral d se of radioactive strontium by rats when it was administered immediately a er the radioactive dose.

CATSCH & MELCHINGER investigated the influence of calcium, magnesium, a d inactive strontium on the retention of radiostrontium administered si ultaneously. Inactive strontium showed a carrier effect even at such a low d se as 30 μM. The greatest effect with a reduction of about 30% of the c ntrols was seen at 187 μM. An increased carrier dose did not give a comparati e reduction, and at 468 μM the control value was attained. The efficiency of calcium was lower than that of strontium, whereas magnesium in high doses reduced the radiostrontium deposition by 30 to 40%. A reduction was also observed with sodium thiosulfate.

The investigations designed to influence the metabolism of incorporated radiostrontium have in many cases given vague results leading to ambiguous conclusions. Hence we considered it to be of great interest to examine the effect of several agents in various concentrations at different times before and after administration of Sr^{90} using a great number of mice.

Materials and Methods

Mice. 1 900 male albino mice weighing between 20 and 22 g were used in our study.

Radiostrontium. A sample of carrier-free strontium-90 in nitric acid solution was neutralized and diluted with 0.9 % sodium chloride solution. Each animal was given 0.2 ml of this solution, containing 10 μC Sr^{90}/ml, by intraperitoneal injection.

Agents. The following agents and doses were given intraperitoneally:

Agents	Concentration	Doses in mM/kg		
$SrCl_2$	0.2 M	1.0	1.5	2.0
Sr-lactate	0.2 M	1.0	1.5	2.0
$CaCl_2$.....	0.2 M	1.0		
Ca-lactate.....	0.2 M	1.0	1.5	
Na-lactate.....	0.2 M	1.0	1.5	2.0
$CaNa_2$-EDTA ..	0.2 M	2.0		
$CaNa_2$-EDTA ..	0.4 M		4.0	8.0
CaNa-citrate ..	0.4 M (citrate)	10.0		

The doses of the various agents are always expressed as millimoles per kilogram bodyweight (mM/kg).

The mixed salt of citric acid was prepared by dissolving calcium hydroxide in a solution of citric acid and NaOH corresponding to the formula $NaH_2C_6H_5O_7$.

Table 1

Retention of Sr^{90} in treated animals (percentage of injected Sr^{90} dose)

Agents	Dose mM/kg	Pre-treatment min.		Early post-treatment min.			Late post-treatment hours				
		30	10	5	10	30	1	2	4	8	24
$SrCl_2$	1	42.7	44.2	42.0	41.5	46.3	45.2	44.0	43.2	53.2	48.
	1.5	48.1	29.9	36.8	36.1	35.7	44.2	42.3	47.5	45.4	50.
	2	39.9	41.4	32.1	40.7	38.4	46.1	49.3	49.4	40.9	44.
Sr-lactate	1	49.1	49.2	41.3	42.4	43.0	47.8	46.1	37.2	44.8	48.
	1.5	44.0	43.9	39.9	44.4	43.2	42.5	55.0	51.2	48.4	57.
	2	42.5	47.7	41.2	49.5	51.6	47.7	52.1	52.0	51.9	54.
$CaCl_2$	1	68.3	64.2	66.4	68.6	61.8	68.9	63.8	65.0	63.8	–
Ca-lactate	1	54.1	67.7	58.1	56.9	63.3	60.4	61.9	56.4	60.1	49.
	1.5	68.1	66.1	51.2	65.8	65.2	63.0	58.1	60.9	66.6	60.
Na-lactate	1	49.5	53.3	59.8	53.5	48.8	59.0	53.3	52.9	50.5	51.
	1.5	51.1	48.8	42.4	48.1	45.0	47.4	48.5	39.1	43.0	53.
	2	58.8	62.8	57.3	55.9	57.8	53.9	52.5	53.2	51.9	52.
$CaNa_2$-EDTA	2	48.0	45.2	50.0	52.2	54.8	51.0	56.4	51.7	45.9	65.
	4	62.7	67.5	47.3	50.8	55.9	51.4	52.5	51.8	55.3	58.
	8	60.8	59.0	55.1	60.0	56.8	55.3	54.6	55.6	57.7	56.
CaNa-citrate	10	49.1	42.3	40.7	42.1	49.9	52.8	64.4	59.1	57.6	57.6
Controls:											
A (before)		45.5	44.8	48.2	48.2	53.1	39.6	47.1	48.4	40.7	51.0
B (after)		54.4	49.8	49.2	46.1	51.9	43.3	46.9	46.6	46.9	55.0

Sodium citrate was added so that the final concentration of citrate became 0.4 M. The Ca/Na ratio was 1:7 and the pH about 6.5. Since the resulting solution is supersaturated with respect to calcium citrate it has to be prepared only a short time before the injections. The higher doses of the calcium salts were too toxic to be used in mice.

Time intervals. The different agents and doses were administered 30 and 10 min before, and 5, 10 and 30 min, and 1, 2, 4, 8 and 24 hours after the injection of Sr^{90}. For each combination 10 mice were used.

Controls. 198 control animals were divided into two groups and received 0.5 ml of 0.9 % sodium chloride solution. The first group was treated at the beginning of the whole experiment and the other one at the end.

Table 2

Retention of Sr^{90} in controls

Dose of 0.9 % NaCl-sol. (ml)	Period of treatment	Number of animals	Retention (% injected dose) ($\bar{x} + SE$)
0.5	Pretreatment.....	40	48.6 ± 1.7
0.5	Early post-treatment	59	49.4 ± 1.3
0.5	Late post-treatment.....	99	46.6 ± 1.0
	Total	198	47.8 ± 0.9

Pretreatment/early post-treatment	t = 0.374
Pretreatment/late post-treatment	t = 1.015
Early post-treatment/late post-treatment	t = 1.707

Methods of analysis. The animals were killed 7 days after the injection of Sr^{90}. The carcasses were ashed in a muffle furnace for 1 hour at 850° C. The ash was dissolved in conc. HNO_3, made up to 50 ml. 0.5 ml of the solutions was transferred to a counting disc of aluminium. All samples were stored for at least 3 weeks in order to obtain equilibrium between Sr^{90} and Y^{90} before counting with a GM-detector and a conventional scaler.

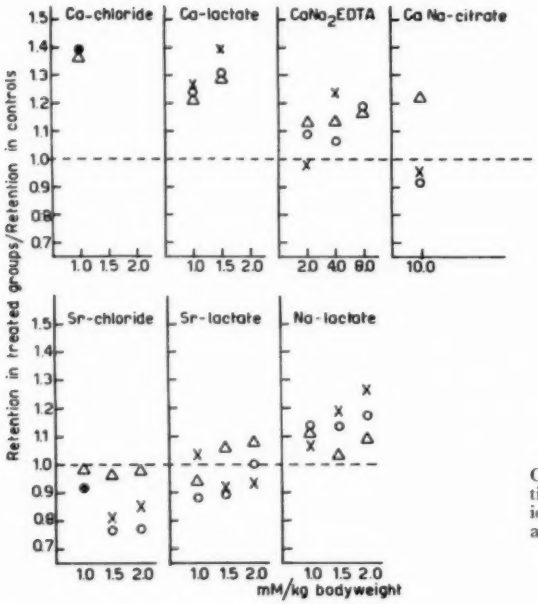
Blanks. Eighteen mice were sacrificed, and 2 μC of Sr^{90} were injected in each body. The animals were ashed and the activity determined as mentioned before.

Results

The results of the experiments are summarized in Table 1. The figures represent the retention expressed in percentage of the injected Sr^{90} dose, after treatment with different concentrations of the agents, given at different intervals before and after the administration of Sr^{90}.

A statistical analysis was attempted in order to find any difference between the various groups reported in the table. No uniform significant difference could, however, be found between the comparatively small primary groups. It was therefore found appropriate to put together the time groups in the following way. Treatment 30 and 10 min before injection of Sr^{90} was designated 'pretreatment', 5, 10 and 30 min after injection 'early post-treatment', and 1, 2, 4, 8 and 24 hours 'late post-treatment'.

The control groups were combined in the same way and, as will be seen from Table 2, the statistical analysis does not show any differences between the various groups. The mean value of all the control groups have been used as the standard value, against which all results from the treated groups have been compared. After regrouping, the results have been statistically treated



Graphs illustrating the effect on retention of radiostrontium with the various agents of different concentrations administered.
× = pretreatment
○ = early post-treatment
△ = late post-treatment

in a way which appears from Table 3 and the graphs shown in the figure above. The t-values and the significance levels are calculated between the standard retention value of the controls and retention of the group in question.

Strontium chloride decreases the retention of Sr^{90} if given as pretreatment or early post-treatment. Late post-treatment has no effect. The best results are obtained with 1.5 and 2.0 mM/kg. An increase of the concentration over 1.5 mM/kg bodyweight does not seem to improve the results.

The effect of strontium lactate is inferior to that of $SrCl_2$. Early post-treatment gives the optimum effect. The calcium sodium citrate seems to have some ability to decrease the deposition of radiostrontium if given as pretreatment or early post-treatment. This effect is, however, of very short duration, i. e. from 10 min before to 10 min after the administration of Sr^{90} (see Table 1). After late post-treatment the retention increases. Both $CaCl_2$ and Ca-lactate significantly increase the retention, independently of the concentrations and times tested. Due to the toxicity of calcium chloride, this substance has only been tested in one concentration. Similar results are obtained with $CaNa_2$-EDTA and Na-lactate. They are, however, not so marked but the increased retention is significant in most groups.

Table 3

Statistical treatment of results

Agent	Dose mM/kg	Period of treatment	No. of mice	Retention (% injected dose) ($\bar{x} \pm SE$)	$\frac{R.T.G.}{R.C.}$	t-values and significance levels
aCl	0.5		198	47.8 ± 0.9	—	—
rontium loride	1.0	Pretreatment	19	43.5 ± 1.7	0.91	2.240[1]
	1.5	»	19	38.5 ± 3.1	0.81	2.879[2]
	2.0	»	20	40.7 ± 1.4	0.85	4.277[3]
	1.0	Early post-treatment	29	43.3 ± 2.0	0.91	2.045[1]
	1.5	» »	29	36.2 ± 1.5	0.76	6.591[3]
	2.0	» »	29	36.9 ± 1.4	0.77	6.527[3]
	1.0	Late post-treatment	50	47.0 ± 1.3	0.98	0.563
	1.5	» »	50	45.9 ± 1.1	0.96	1.338
	2.0	» »	47	46.4 ± 1.5	0.97	0.795
Strontium lactate	1.0	Pretreatment	20	49.2 ± 1.8	1.03	0.697
	1.5	»	20	43.9 ± 1.3	0.92	2.468[1]
	2.0	»	20	45.1 ± 1.9	0.94	1.286
	1.0	Early post-treatment	30	42.2 ± 1.5	0.88	3.200[2]
	1.5	» »	28	42.7 ± 1.7	0.89	2.656[2]
	2.0	» »	27	47.9 ± 2.1	1.00	0.044
	1.0	Late post-treatment	50	44.9 ± 1.4	0.94	1.747
	1.5	» »	50	50.9 ± 1.1	1.06	2.183[1]
	2.0	» »	49	51.6 ± 1.2	1.08	2.533[1]
Calcium chloride	1.0	Pretreatment	20	66.2 ± 2.2	1.38	7.73[3]
	1.0	Early post-treatment	28	66.9 ± 2.1	1.38	8.34[3]
	1.0	Late post-treatment	31	65.2 ± 1.8	1.36	8.66[3]
Calcium lactate	1.0	Pretreatment	20	60.9 ± 2.8	1.27	4.456[3]
	1.5	»	20	67.1 ± 2.4	1.40	7.539[3]
	1.0	Early post-treatment	30	59.4 ± 2.1	1.24	3.066[3]
	1.5	» »	28	62.8 ± 2.0	1.31	6.818[3]
	1.0	Late post-treatment	50	57.7 ± 1.6	1.21	5.380[3]
	1.5	» »	47	61.8 ± 1.3	1.29	8.861[3]
Sodium lactate	1.0	Pretreatment	20	51.4 ± 1.6	1.07	1.957
	1.5	»	20	56.9 ± 2.2	1.19	3.824[1]
	2.0	»	20	60.8 ± 2.2	1.27	5.462[3]
	1.0	Early post-treatment	30	54.0 ± 1.7	1.13	3.229[2]
	1.5	» »	29	54.2 ± 1.8	1.13	3.168[2]
	2.0	» »	29	55.9 ± 1.7	1.17	4.219[3]
	1.0	Late post-treatment	50	53.4 ± 1.1	1.11	3.944[3]
	1.5	» »	49	49.3 ± 1.7	1.03	0.777
	2.0	» »	48	52.8 ± 1.3	1.09	3.165[2]

R.T.G. = Retention in treated groups; R.C. = Retention in controls.
[1] $p < 0.05$. — [2] $p < 0.01$. — [3] $p < 0.001$.

Table 3 (Cont.)

Agent	Dose mM/kg	Period of treatment	No. of mice	Retention (% injected dose) ($\bar{x} \pm SE$)	R.T.G./R.C.	t-values and significance levels
$CaNa_2$-EDTA	2.0	Pretreatment	19	46.7 ± 2.1	0.98	0.480
	4.0	»	17	59.2 ± 2.6	1.24	4.145 [3]
	8.0	»	19	59.9 ± 1.4	1.25	7.246 [3]
	2.0	Early post-treatment	30	52.3 ± 1.3	1.09	2.848 [2]
	4.0	» »	29	51.0 ± 1.6	1.07	1.711
	8.0	» »	30	57.1 ± 1.7	1.19	4.844 [3]
	2.0	Late post-treatment	50	54.0 ± 1.5	1.13	3.543 [1]
	4.0	» »	50	53.9 ± 1.2	1.13	4.067 [3]
	8.0	» »	50	55.8 ± 1.3	1.17	5.063 [3]
CaNa-citrate	10.0	Pretreatment	20	45.7 ± 1.6	0.96	1.556
	10.0	Early post-treatment	30	44.2 ± 0.9	0.92	2.835 [1]
	10.0	Late post-treatment	49	58.3 ± 1.0	1.22	7.778 [3]

[1] $p < 0.05$. — [2] $p < 0.01$. — [3] $p < 0.001$.

Conclusion

Among previous attempts to influence the elimination of radiostrontium, MacDonald and Catsch & Melchinger have succeeded in decreasing the skeletal retention of strontium 90 by the injection of inactive strontium salts in rats. In their investigations, an effect was only seen if the stable strontium was given practically simultaneously with Sr^{90}.

Catsch & Melchinger tried increasing doses of stable strontium. They found that the effect was not linear. With high doses a relative increase in the skeletal retention was observed.

In our investigation a significant decrease in the skeletal deposition of Sr^{90} was obtained if stable strontium was injected within half an hour before or after the administration of Sr^{90}. An optimum effect was seen with 1.5 mM/kg of a strontium salt, whereas 2 mM/kg did not increase the effect. Our studies in mice thus confirmed the results of previous investigations in rats with regard to the effect of inactive strontium on the deposition of Sr^{90}.

The effect of non-radioactive strontium salts is apparently a carrier effect, and, as late post-treatment has no effect, a release of radiostrontium already fixed in the skeleton cannot be expected.

Earlier investigations on the effect of calcium are more inconsistent. In MacDonald's study, injected calcium significantly increased the retention of Sr^{90}, while Spencer et coll. succeeded in obtaining a significant increase

of the excretion of Sr^{90}. CATSCH & MELCHINGER state that they obtained a decreased retention with calcium. The effect was, however, lower than that of strontium.

In our investigation there is a highly significant increased retention of Sr^{90} when calcium chloride and calcium lactate were injected, independent of time and concentration. Our results with calcium are in good agreement with those of MACDONALD.

SPENCER et coll. measured the excretion, not the retention. The significance of the results of CATSCH & MELCHINGER is not convincing.

The results with calcium salts are more difficult to assess but the following tentative interpretation is made.

In normal blood serum the concentration of free calcium ions is about one half of the total amount of calcium, the other part consisting of complexes with proteins and acids (NEUMAN & NEUMAN 1958). The corresponding data for strontium are not so well known. It might, however, be expected that relatively more strontium is in the ionic form due to the usually weaker Sr complexes. Studies in vitro (NEUMAN) have shown that with increasing concentrations of Ca, less Sr was incorporated by the solid phase of a synthetic hydroxyapatite preparation. The significant increase in the retention of Sr^{90} with an increased Ca dose in our study, however, is observed in a not well-defined system and under non-equilibrium conditions. The effects of Ca in this case cannot be explained by a simple carrier or dilution mechanism but must be due to some physiologic properties of the living animal. All equilibria between Ca and Sr and the various complex-forming agents will be influenced by changing Ca concentrations. An increasing Ca concentration will promote the decomposition of the Sr complexes, thus increasing the amount of free Sr ions. This might only be a part of the actual mechanism, since there are other phenomena involved, like adsorption and diffusion, which are difficult to explain. The opposite effect of calcium, usually reported from peroral and dietary experiments, is probably due to the rather well established discrimination against strontium by the intestines and kidneys.

With regard to the effect of different complexing agents on the elimination of radiostrontium the best results have been reported with zirconium citrate (COHN and GONG, CATSCH & MELCHINGER) and sodium calcium citrate (ITO & TSURUFUJI). Mixed calcium and sodium salts of EDTA (COHN & GONG, VAUGHAN & TUTT) had no effect on the excretion of Sr^{90}.

ITO & TSURUFUJI have also reported a decrease of the radiostrontium deposition after some weak chelating agents, among other lactates.

In our investigation, calcium sodium citrate has shown some ability to decrease the deposition of radiostrontium. $CaNa_2$-EDTA and Na-lactate have the opposite effect and it is interesting to see that Sr-lactate has a lower effect than $SrCl_2$.

The inconsistent results obtained with different complexing agents in

our study could be explained by the calculations made by SCHUBERT (1953) which show that there are no hopes, not even theoretical, of decreasing the amount of free Sr in the bloodstream by using strong chelating agents like EDTA or weak ones such as lactic acid. By administration of large doses of moderately strong complexing agents, e. g. citric acid, it would be possible to bind 80 % of the circulating Sr despite the fact that citrate binds Ca twice as strongly as Sr. These calculations refer to ideal conditions, which may not be fully valid in the physiologic state. The increased retention with $CaNa_2$-EDTA in this study is in agreement with the results of CATSCH et coll. who used the more toxic sodium salt. One possibility, which should not be overlooked, is that the formation of soluble Sr complexes may facilitate the transport of the isotope to the vicinity of the bone crystals.

An interesting result has been observed concerning the time intervals. In general, early post-treatment gives somewhat lower retention values than pretreatment but this effect is not significant.

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SUMMARY

The effect of $SrCl_2$, Sr-lactate, $CaCl_2$, Ca-lactate, Na-lactate, $CaNa_2$-EDTA and $CaNa_2$-citrate on the deposition of radiostrontium has been examined in mice. Of the tested agents, only strontium salts and calcium sodium citrate were able to decrease the retention if given within half an hour before or after the administration of radiostrontium. The optimum effect was obtained with $SrCl_2$; the effect of Sr-lactate was less. All the other agents increased the retention.

ZUSAMMENFASSUNG

Die Wirkung von $SrCl_2$, Sr-laktat, $CaCl_2$, Ca-laktat, Na-laktat, $CaNa_2$-EDTA und $CaNa_2$-citrat wurde auf die Ablagerung von Radiostrontium bei Mäusen geprüft. Von den geprüften Mitteln waren nur Strontiumsalze und Calcium-Natriumcitrat imstande, die Retention herabzusetzen, vorausgesetzt, dass sie innerhalb einer halben Stunde vor oder nach der Verabreichung von Radiostrontium gegeben wurden. Die optimale Wirkung wurde mit $SrCl_2$ erreicht. Die Wirkung von Sr-laktat war geringer. Alle die übrigen Mittel erhöhten die Retention.

RÉSUMÉ

Les auteurs ont étudié sur des souris l'effet du $SrCl_2$, du lactate de Sr, du $CaCl_2$, du lactate de Ca, du lactate de Na, du $CaNa_2$-EDTA et du citrate de $CaNa_2$ sur la fixation du radiostrontium. Parmi les agents étudiés, seuls les sels de strontium et le citrate de calcium-sodium sont capables de diminuer la fixation du radiostrontium quand ils sont administrés une demi-heure avant ou après celui-ci. L'effet optimum était obtenu avec $SrCl_2$. L'effet du lactate de Sr était moindre. Tous les autres agents ont augmenté la fixation.

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BOOK REVIEWS

HEALTH PHYSICS INSTRUMENTATION. By John S. Handloser. (International Series of Monographs on Nuclear Energy. Div. V, Vol. 1). 182 pages, 24 tables, 100 illustrations. Pergamon Press, London-Oxford-New York-Paris 1959. Price: 42 shillings.

The commonly used, though in fact rather misleading, term 'health physics' (somewhat more fitting ones might be 'radiation protection physics' or 'radiation hygiene') covers a subject which has grown enormously during less than two decades. The aim of this work, which has expanded with the development of nuclear power and weapons and the increasing use of radioisotopes and other sources of radiation, is to offer protection against the untoward effects of radiation not only to those working directly with radiation but also to all those who, often unknowingly, are exposed to it. It consequently concerns more or less the whole of humanity. Natural sciences such as physics, chemistry, meteorology, geology and hydrography, as well as biology and medicine (including genetics and radiology), all play their part in this field. As the dangerous radiations are imperceptible to the senses, reliance must be placed on various instruments to detect and measure the hazards and to check the adequacy of protection devices and measures. The present book consists of a review of the more important instrument types.

In order to facilitate the understanding of the modes of action of radiation and of the operation of various types of instruments, the elements of radiation physics, radiation dosimetry, and currently accepted maximum permissible doses are surveyed. This section is, however, too brief to be of real help to novices in the field. The present views regarding permissible doses and the fact that the weekly dose has lost its dominating position to doses accumulated over longer periods have not been included.

After this introduction follow chapters on radiation detectors (ion chambers, proportional and GM counters, scintillation counters), portable and fixed measuring instruments using these detectors, neutron measurements, the construction and equipment of measurement laboratories, and methods to calibrate instruments, as well as personnel monitoring by means of film badges, pocket chambers, etc. The principles of the more important instruments are described and many practical hints on the use of the latter are given. The limited space in the book and the large subject matter have, however, unavoidably caused many matters to be somewhat cursorily treated: methods of controlling radioactive waste disposal are, for example, scarcely mentioned. But on the whole, the book can be recommended as a good general introduction to the subject, to be supplemented for special needs by more detailed treatises, many of which are included in the references.

Sven Benner

ELEKTROKYMOGRAPHIE. Von Karl Heckmann. 140 Abbildungen, 123 Seiten. Springer Verlag, Berlin, Göttingen, Heidelberg 1959. Price: DM 49.80.

This book has the characteristics of a monograph, being a presentation of both the author's personal experiences and observations reported in the literature in the study of the diseased and normal heart by electrokymography. The introductory sections are devoted to a description of the mode of action of electrokymography. The pulsations of the heart chambers and great blood vessels under normal conditions are described in detail, much importance being placed upon so-called phase analysis for the interpretation of the stages of movement connected with the motion of the heart as a whole and the resulting displacement of the 'mass centre' during the cardiac cycle.

Like most other investigators the author uses the electrocardiogram as a reference curve, and to some extent also the heart sounds. In so far as comparisons are made with the pressure conditions the latter are illustrated by schematic drawings and not by actual recordings.

The electrokymographic findings in acquired and congenital heart defects are mainly described in connection with analyses of the pathologic movement patterns in the ventricles, atria and great vessels. Various types of rhythm disturbance are also described.

The author's most notable, and most original, contribution seems to be the examination of the different components in the cardiac pulsations, which are a combination of pendulum and rotation movements. The method is based on the recording of the motion of the cardiac silhouette and great vessels by means of both 'slit kymography' and electrokymography, curves being registered over a great many parts of the heart outline. With this technique it is possible to determine the displacement of the cardiac silhouette during the heart cycle and to obtain an explanation of many of the paradoxical movements in the electrokymogram that cannot be ascribed to pressure and volume changes in the heart chambers or the great vessels. The author concludes as a result of his investigations that among all the known heart movements, rotation around the longitudinal axis of the heart is the only one not determinable by this method.

The most exhaustive part of the book deals with the movement phenomena in different heart defects. The observations coincide in general with those of the reviewer. The sections on constrictive pericarditis and pulmonary hypertension are the best, in the reviewer's opinion, but as the size and composition of the material from which the conclusions are drawn is seldom stated it is not always easy for the reader to decide to what degree the electrokymographic changes described may possess general diagnostic significance in the various heart defects. In patent ductus arteriosus, the observations refer only to cases with a pressure increase in the pulmonary circulation. It would have been valuable if the author had placed more emphasis on the fact that such cases represent only a small fraction of the total cases of this defect, seeing that the electrokymograms are as a rule normal in cases where the shunt is small and there is little or no increase in pressure. This is also the case with other heart defects treated by the author, such as atrial septal defect and ventricular septal defect.

When the author asserts, with Haubrich, that it is far from always possible to distinguish between mitral stenosis and mitral insufficiency by electrokymography his statement is no doubt correct; the clinical problem is, however, seldom a question of this difficulty but rather of deciding to what extent a stenosis is complicated by a significant insufficiency in the mitral valve. According to the reviewer's experience, cases with absolutely typical 'stenosis curves' may prove at operation to be combined with obvious regurgitation. It would also seem essential to stress that, strictly speaking, such curves are only a reflection of an obstruction to the evacuation of the atrium and that they may have the same general shape irrespective of the etiology of the obstruction.

The work would have been improved if greater consideration had been paid to the functional anatomy of the individual heart chambers as it appears in rapid angiocardiography. This would have been especially valuable in the analysis of the infundibulum of the right ventricle and of the outflow region in the left ventricle.

Although objections may be raised on various points the book may nevertheless be regarded as the best review of the methods, aims, and fields of application of electrokymography at present available in the sphere of cardiology. The references are extensive, and a large number of well-reproduced electrokymograms, diagrams, and drawings increase the value of the work.

Ulf Rudhe

KLINISCHE RÖNTGENDIAGNOSTIK CHIRURGISCHER ERKRANKUNGEN. Von Hans Oberhoff, Heinz Vieten und Hermann Karcher. 1050 Seiten, 122 Abbildungen. Springer, Berlin 1959. Price: DM 398.

This is a very comprehensive work by three authors. The first and greater part deals with pure technique as well as with diseases of the internal organs and this is written by VIETEN, a roentgenologist. An additional urological chapter is by DETTMAR, who is a urologist. The second part, which concerns the skeleton, is written by OBERFDAHLHOFF and KARCHER, who are surgeons. The authors state that the book is intended to serve a double purpose; to inform the roentgenologist about the special intentions of the surgeon and to show the surgeon various roentgenologic achievements. It would not perhaps be unreasonable to expect a book on diagnostic roentgenology to be written by roentgenologists and not by other specialists. Some shortcomings of the book, from the radiologic standpoint, may be due to the fact that three of the authors are not roentgenologists.

As to the actual book this in many ways gives a complete summary of surgical conditions in which the roentgen examination is decisive in the diagnosis. Some chapters, for instance those on thoracic diseases and lesions of the intestinal tract, are both comprehensive and accurate and contain many good illustrations. The conditions described are, however, mostly commonplace, the technique conveys the impression of not being quite up to date, and one does not seem to learn anything new. The chapter on the acute abdomen is of limited value, and to find in the urological part that most of the examinations are confined to retrograde pyelographies and that renal diagnoses are presented without angiographies provokes astonishment. The second part covering osteology makes generally good reading and includes the pathology of lesions commonly encountered in larger clinics.

Although the book may be of value to other readers it offers hardly anything new of interest to an experienced roentgenologist.

J. Frimann-Dahl

DIAGNOSIS OF CONGENITAL HEART DISEASE. 2nd Edition. By S. R. Kjellberg, E. Mannheimer, U. Rudhe and B. Jonsson. 866 pages, 727 illustrations. The Year Book Publishers, Chicago 1959. Price: $ 28.

The material of 396 cases of congenital heart disease which formed the basis of the first edition of this book has been more than doubled in this present second edition. New types of congenital heart disease have been included and in many cases new investigation methods have been adopted and earlier procedures modified. One or two errors in the first edition have been corrected and four completely new chapters have been added. Several conditions, such as atrial septal defects and anomalous drainage of the pulmonary veins, have been subjected to detailed investigations. The four new chapters deal with pulmonary atresia with an intact ventricular septum, stenosis or atresia of branches of the pulmonary artery, the communication between the left atrium and coronary sinus, and corrected transposition of the great vessels, respectively. The chapters on the embryology and on the roentgen anatomy and physiology of the heart have been considerably extended.

The book in its second edition has the same merits as previously and is probably indispensable in cardiologic centres as well as in all roentgen departments specializing in heart diagnostics. From the purely roentgenologic viewpoint it may possibly be said that too much space has been devoted to electrokymography, a factor which contributes towards making the volume unnecessarily bulky. It must be remembered that at the time

of the appearance of the first edition, electrokymography had a greater theoretical and practical value than it has to-day. The amount of knowledge presented in the book cannot fail to impress the reader and the enormous output of work involved in its publication is worthy of universal admiration.

Gunnar Jönsson

DAS RÖNTGENSCHICHTBILD. Von A. Gebauer, E. Muntean, E. Stutz und H. Vieten. 446 Seiten, 699 Abbildungen. Georg Thieme, Stuttgart 1959. Price: 148 DM.

Tomography has by now achieved an established place in the routine of roentgen diagnostics. The literature on the subject is abundant but is largely concerned with details of theory and practice and the non-specialist finds it difficult to obtain a broad view. This monograph fulfills the want in providing a general survey of the method. Part I contains a detailed account of the theory of tomography, and part II, the clinical section, includes examples of its application in examinations of the bones, of the throat, thorax and abdomen, and of the central nervous system. The diagnostic importance of tomography is illustrated by numerous tomograms, many derived from the authors' own case material.

One can only regret, with the authors, that they work only with apparatus of the unidirectional type, and that all the tomograms reproduced in the clinical section are the result of unidirectional movement. It would have been desirable in a work such as this to offer more than merely theoretical evidence of the superiority of hypocycloid blurring. Tomography of this kind gives better results, especially in the examination of bones, as the authors mention.

The organs of the thorax are the classical field of application of tomography and in this monograph occupy a predominant place. The cases are illustrated in a highly instructive way and numerous transverse tomograms are included. The importance of tomographic analysis in congenital and acquired anomalies of the heart would, however, seem to be doubtful, except in extremely rare cases.

As regards the central nervous system, the reviewer was unable to find examples of the application of the method in gas myelography, a very common investigation in Scandinavia and one of the most rewarding fields of tomography.

The above views apart, the monograph is a welcome addition to the tomographic literature. The illustrations are largely of good quality and there are plenty of references. The book is warmly recommended.

Stig Fagerberg

ANGIOGRAPHIC STUDIES OF THE ANATOMY OF SINGLE AND MULTIPLE RENAL ARTERIES. By Erik Boijsen. 135 pages, 56 illustrations and 16 tables. Acta radiol. (1959) Suppl. No. 183. Price: Sw. Kr. 30: —.

The anatomy of the renal artery was investigated by angiography in a large clinical material and in kidneys removed at autopsy.

Variations are shown in the origin and course of the single renal artery from the aorta to the renal hilum. The single renal artery divides into a ventral and a dorsal artery. These vessels may be defined arteriographically in a single frontal projection because of their characteristic course and distribution in the renal parenchyma. The importance of the exact definition of these vessels is stressed. All branches of the single renal artery or of the ventral and dorsal arteries have circumscribed regional supplies, for the definition of which the kidney

is divided into four segments. The segmental division of the kidney is based on the normal intrarenal arrangements of the pyramids. These segments may be demonstrated during the nephrographic phase when the hilum and the columns of Bertin as well as the sulci on the kidney surface are outlined. The normal variations in the supply of the four segments are described. The variations are greater than formerly supposed, which in part is due to the fact that previous anatomic studies did not take into consideration the varying arrangement of the pyramids in the kidney.

The frequency of multiple renal arteries is studied, as well as the origin, course, and region of supply of the supplementary arteries. These arteries, like the branches of the single renal artery, are segmental arteries, although they arise higher up, i. e. from the aorta. Special attention is given to the lower polar artery, which is the most common and most important of all the supplementary arteries.

The anatomy of arteries arising from the renal artery or its branches and which supply adjacent renal structures (the fatty capsule, suprarenal gland, and renal pelvis) is studied and the appearances in some common renal disorders are described.

Autoreview